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(54) **REMEDIES OR PREVENTIVES FOR DISEASES IN ASSOCIATION WITH CHEMOKINES**

HEILMITTEL UND VORBEUGUNG FÜR MIT CHEMOKINEN VERBUNDENEN ERKRANKUNGEN
MOYENS DE TRAITEMENT ET DE PREVENTION CONTRE LES MALADIES ASSOCIEES A DES
CHIMIOKINES

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(73) Proprietor: **TEIJIN LIMITED**
Osaka-shi Osaka 541-0054 (JP)

(72) Inventors:
• **SHIOTA, Tatsuki Teijin Limited**
Hino-shi, Tokyo 191-0065 (JP)
• **MIYAGI, Fuminori Teijin Limited**
Hino-shi, Tokyo 191-0065 (JP)
• **KAMIMURA, Takashi Teijin Limited**
Hino-shi, Tokyo 191-0065 (JP)
• **OHTA, Tomohiro Teijin Limited**
Hino-shi, Tokyo 191-0065 (JP)

• **TAKANO, Yasuhiro Teijin Limited**
Hino-shi, Tokyo 191-0065 (JP)
• **HORIUCHI, Hideki Teijin Limited**
Hino-shi, Tokyo 191-0065 (JP)

(74) Representative: **Hallybone, Huw George et al**
Carpmaels and Ransford,
43 Bloomsbury Square
London WC1A 2RA (GB)

(56) References cited:
EP-A1- 0 217 286 **WO-A-00/69815**
WO-A-99/25686 **WO-A1-00/31032**
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• **KHALID M. ET AL.: 'N,N'-disubstituted**
L-isoglutamines as novel cancer
chemotherapeutic agents' DRUGS EXP. CLIN.
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Description

Technical Field

5 **[0001]** The present invention relates to cyclic amine derivatives and more particularly it relates to the use of chemokine receptor antagonists in the manufacture of medicaments for treating glomerulonephritis, interstitial nephritis or nephrotic syndrome.

Background Art

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[0002] Chemokines are a generic name of a group of inflammatory/immunomodulatory polypeptides having a molecular weight of 6 to 15 KD and produced in inflammatory sites by various kinds of cells, for example, macrophages, monocytes, eosinophils, neutrophils, fibroblasts, vascular endothelial cells, smooth muscle cells and mast cells. The chemokines are classified into two major subgroups of CXC chemokines (or α -chemokines) and CC chemokines (or β -chemokines) by the common location of four preserved cysteine residues and a difference in chromosomal locations of genes encoding the chemokines. The first two cysteines of the CXC chemokines are separated by one amino acid; however, the same cysteines of the CC chemokine are adjacent. For example, IL-8 (an abbreviation for interleukin-8) is the CXC chemokines. On the other hand, MIP-1 α/β (an abbreviation for macrophage inflammatory protein-1 α/β), MCP-1 (an abbreviation for monocyte chemoattractant protein-1) and RANTES (an abbreviation for regulated upon activation, normal T-cell expressed and secreted) are cited as the CC chemokines.

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[0003] Furthermore, there also exist chemokines which do not fall into either of chemokine subgroups. Lymphotactin having only two cysteines and classified as C chemokines and fractalkine classified as CX3C chemokines because the first two cysteines are separated by three amino acids and having a chemokine-like domain in the mucin structure are cited as such a chemokine. The chemokines promote cell migration and have expression enhancing actions on cellular adhesion molecules such as integrins and further cellular adhesion enhancing actions. Therefore, the chemokines are thought to be protein factors closely involved in the adhesion and infiltration of leukocytes or the like into the pathogenic sites such as inflammatory tissues. See, for example, The Chemokine Facts Book, by Vaddi, K. et al., Academic Press, 1997; Chemoattractant Ligand and Their Receptors, edited by Horuk, R., CRC Press, 1996; Ward, G. W. et al., Biochem. J., 1998, 333, 457; Luster, A. D., New Engl. J. Med., 1998, 338, 436; Bagglioni, M., Nature, 1998, 392, 565; Rollins, B. J., Blood, 1997, 90, 909; Alam, R., J. Allergy Clin. Immunol., 1997, 99, 273; Hancock, W. W., Am. J. Pathol., 1996, 148, 681; Taub, D. D., Cytokine & Growth Factor Rev., 1996, 7, 335; Strieter, R. M. et al., J. Immunol., 1996, 156, 3583; Furie, M. B. et al., Am. J. Pathol., 1995, 146, 1287; Schall, T. J. et al., Current Opinion in Immunology, 1994, 6, 865; and Edginton, S. M., Biotechnology, 1993, 11, 676 as references.

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[0004] For example, MIP-1 α causes a transient increase in intracellular calcium ion concentration levels and induces cell migration of T lymphocytes or B lymphocytes (see, for example, Tabu, D. D. et al., Science, 1993, 260, 355 and Shall, T. J. et al., J. Exp. Med., 1993, 177, 1821), cell migration of eosinophils (see, for example, Rot, A. et al., J. Exp. Med., 1992, 176, 1489), cell migration of NK cells (see, for example, Magazachi, A. A. et al., J. Immunol., 1994, 153, 4969), expression of integrins (see, for example, Vaddi, K. et al., J. Immunol., 1994, 153, 4721) and differentiation of osteoclasts (see, for example, Kukita, T. et al., Lab. Invest., 1997, 76, 399). MIP-1 α also increases the IgE and IgG4 production in B cells (see, for example, Kimata, H. et al., J. Exp. Med., 1996, 183, 2397) and inhibits the proliferation of hematopoietic stem cells (see, for example, Mayani, H. et al., Exp. Hematol., 1995, 23, 422; Keller, J. R. et al., Blood, 1994, 84, 2175; Eaves, C. J. et al., Proc. Natl. Acad. Sci. USA, 1993, 90, 12015; Bodine, D. M. et al., Blood, 1991, 78, 914; and Broxmeyer, H. E. et al., Blood, 1990, 76, 1110).

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[0005] As to the association of MIP-1 α with in vivo actions or pathogenesis of diseases, it has been reported that the MIP-1 α is a pyrogen in rabbits (see, for example, Davatelis, G. et al., Science, 1989, 243, 1066) and the injection of the MIP-1 α into the footpads of mice results in inflammatory reactions such as infiltration of neutrophils or mononuclear cells (see, for example, Alam, R. et al., J. Immunol., 1994, 152, 1298).

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[0006] It has been also reported that a neutralizing antibody to MIP-1 α has inhibitory effects or remedial effects in animal models of granuloma (see, for example, Lukacs, N. W. et al., J. Exp. Med., 1993, 177, 1551), asthma (see, for example, Lukacs, N. W. et al., Eur. J. Immunol., 1995, 25, 245 and Lukacs, N. W. et al., J. Immunol., 1997, 158, 4398), multiple sclerosis (see, for example, Karpus, W. J. et al., J. Immunol., 1995, 155, 5003 and Karpus, W. J. et al., J. Leukoc. Biol., 1997, 62, 681), idiopathic pulmonary fibrosis (see, for example, Smith, R. E. et al., J. Immunol., 1994, 153, 4704 and Smith, R. E., Biol. Signals, 1996, 5, 223), acute lung injury (see, for example, Shanley, T. P. et al., J. Immunol., 1995, 154, 4793 and Standiford, T. J. et al., J. Immunol., 1995, 155, 1515) and rheumatoid arthritis (see, for example, Kasama, T. et al., J. Clin. Invest., 1995, 95, 2868) and the like. Furthermore, it has been reported that coxsackie virus infection-induced myocarditis or herpes stromal keratitis is inhibited in MIP-1 α gene deficient mice (see, for example, Cook, D. N. et al., Science, 1995, 269, 1583 and Tumpey, T. M. et al., J. Virology, 1998, 72, 3705).

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[0007] In addition, significant expression of MIP-1 α was recognized in patients such as chronic pulmonary inflam-

matory diseases (see, for example, Standiford, T. J. et al., J. Immunol., 1993, 151, 2852), hypersensitivity pneumonitis (see, for example, Denis, M., Am. J. Respir. Crit. Care Med., 1995, 151, 164), rheumatoid arthritis (see, for example, Koch, A. E. et al., J. Clin. Invest., 1994, 93, 921), infectious meningitis (see, for example, Lahrtz, F. et al., J. Neuroimmunol., 1998, 85, 33) and chronic inflammation of muscle (see, for example, Adams, E. M. et al., Proc. Assoc. Am. Physicians, 1997, 109, 275). The studies indicate that MIP-1 α is deeply involved in the local accumulation of various subtypes of leukocytes in association with initiation, progression and maintenance of inflammatory diseases.

[0008] MCP-1 [also known as MCAF (an abbreviation for macrophage chemotactic and activating factor) or JE] is a CC chemokine produced by monocytes/macrophages, smooth muscle cells, fibroblasts and vascular endothelial cells and has a cell migration activity and cell adhesion enhancing actions on monocytes (see, for example, Valente, A. J. et al., Biochemistry, 1988, 27, 4162; Matsushima, K. et al., J. Exp. Med., 1989, 169, 1485; Yoshimura, T. et al., J. Immunol., 1989, 142, 1956; Rollins, B. J. et al., Proc. Natl. Acad. Sci. USA, 1988, 85, 3738; Rollins, B. J. et al., Blood, 1991, 78, 1112; Jiang, Y. et al., J. Immunol., 1992, 148, 2423; and Vaddi, K. et al., J. Immunol., 1994, 153, 4721), memory T lymphocytes (see, for example, Carr, M. W. et al., Proc. Natl. Acad. Sci. USA, 1994, 91, 3652), T lymphocytes (see, for example, Loetscher, P. et al., FASEB J., 1994, 8, 1055) and natural killer cells (NK cells) (see, for example, Loetscher, P. et al., J. Immunol., 1996, 156, 322 and Allavena, P. et al., Eur. J. Immunol., 1994, 24, 3233) or the like and MCP-1 further has actions as a histamine releasing factor from basophils (see, for example, Alam R. et al., J. Clin. Invest., 1992, 89, 723; Bischoff, S. C. et al., J. Exp. Med., 1992, 175, 1271; and Kuna, P. et al., J. Exp. Med., 1992, 175, 489).

[0009] Moreover, remarkable expression of MCP-1 has been reported in diseases in which the accumulation of monocytes/macrophages and/or T cells is thought to be deeply involved in initiation, progression and maintenance of lesions such as atherosclerosis (see, for example, Hayes, I. M. et al., Arterioscler. Thromb. Vasc. Biol., 1998, 18, 397; Takeya, M. et al., Hum. Pathol., 1993, 24, 534; Yla-Herttuala, S. et al., Proc. Natl. Acad. Sci. USA, 1991, 88, 5252; and Nelken, N. A., J. Clin. Invest., 1991, 88, 1121), rheumatoid arthritis (see, for example, Koch, A. E. et al., J. Clin. Invest., 1992, 90, 772; Akahoshi, T. et al., Arthritis Rheum., 1993, 36, 762; and Robinson, E. et al., Clin. Exp. Immunol., 1997, 101, 398), nephritis (see, for example, Noris, M. et al., Lab. Invest., 1995, 73, 804; Wada, T. et al., Kidney Int., 1996, 49, 761; and Gesualdo, L. et al., Kidney Int., 1997, 51, 155), nephropathy (see, for example, Saitoh, A. et al., J. Clin. Lab. Anal., 1998, 12, 1; Yokoyama, H. et al., J. Leukoc. Biol., 1998, 63, 493), pulmonary fibrosis and pulmonary sarcoidosis (see, for example, Sugiyama, Y. et al., Internal Medicine, 1997, 36, 856), asthma (see, for example, Karina, M. et al., J. Invest. Allergol. Clin. Immunol., 1997, 7, 254; Stephane, T. H., Am. J. Respir. Crit. Care Med., 1997, 156, 1377; and Sousa, A. R. et al., Am. J. Respir. Cell Mol. Biol., 1994, 10, 142), multiple sclerosis (see, for example, McManus, C. et al., J. Neuroimmunol., 1998, 86, 20), psoriasis (see, for example, Gillitzer, R. et al., J. Invest. Dermatol., 1993, 101, 127), inflammatory bowel disease (see, for example, Grimm, M. C. et al., J. Leukoc. Biol., 1996, 59, 804 and Reinecker, H. C. et al., Gastroenterology, 1995, 106, 40), cardiomyopathy (see, for example, Seino, Y. et al., Cytokine, 1995, 7, 301), endometriosis (see, for example, Jolicœur, C. et al., Am. J. Pathol., 1998, 152, 125), intra-peritoneal adhesion (see, for example, Zeyneloglu, H. B. et al., Human Reproduction, 1998, 13, 1194), congestive heart failure (see, for example, Aurust, P. et al., Circulation, 1998, 97, 1136), chronic liver disease (see, for example, Marra, F. et al., Am. J. Pathol., 1998, 152, 423), viral meningitis (see, for example, Lahrtz, F. et al., Eur. J. Immunol., 1997, 27, 2484), Kawasaki disease (see, for example, Wong, M. et al., J. Rheumatol., 1997, 24, 1179) and sepsis (see, for example, Salkowski, C. A. et al., Infect. Immun., 1998, 66, 3569).

[0010] The inhibitory effects or remedial effects of an anti-MCP-1 antibody have been reported in animal models such as rheumatoid arthritis (see, for example, Schimmer, R. C. et al., J. Immunol., 1998, 160, 1466; Schrier, D. J., J. Leukoc. Biol., 1998, 63, 359; and Ogata H. et al., J. Pathol., 1997, 182, 106), multiple sclerosis (see, for example, Karpus, W. J., J. Leukoc. Biol., 1997, 62, 681), nephritis (see, for example, Lloyd, C. M. et al., J. Exp. Med., 1997, 185, 1371 and Wada T. et al., FASEB J., 1996, 10, 1418), asthma (see, for example, Gonzalo, J.-A. et al., J. Exp. Med., 1998, 188, 157 and Lukacs, N. W., J. Immunol., 1997, 158, 4398), atherosclerosis (see, for example, Guzman, L. A. et al., Circulation, 1993, 88 (suppl.), I-371), delayed type hypersensitivity (see, for example, Rand, M. L. et al., Am. J. Pathol., 1996, 148, 855), pulmonary hypertension (see, for example, Kimura, H. et al., Lab. Invest., 1998, 78, 571) and intraperitoneal adhesion (see, for example, Zeyneloglu, H. B. et al., Am. J. Obstet. Gynecol., 1998, 179, 438).

[0011] Further, it has been reported that MCP-1 (9-76) which is a peptide antagonist of MCP-1 inhibits arthritis in the mouse model (see, for example, Gong, J.-H., J. Exp. Med., 1997, 186, 131) and that MCP-1 is essential to monocyte mobilization in vivo in studies on MCP-1 gene deficient mice (see, for example, Lu, B. et al., J. Exp. Med., 1998, 187, 601 and Gu, L. et al., Moll. Cell, 1998, 2, 275).

[0012] These data indicate that chemokines such as MIP-1 α and MCP-1 accumulate monocytes, lymphocytes or the like in disease sites and activate the cells and thus strongly suggest that the chemokines are deeply associated with initiation, progression and maintenance of diseases wherein monocytes, lymphocytes and the like are assumed to be deeply associated with the progression of lesion, for example, atherosclerosis, rheumatoid arthritis, psoriasis, asthma, ulcerative colitis, nephritis (nephropathy), multiple sclerosis, pulmonary fibrosis, myocarditis, hepatitis, pancreatitis, sarcoidosis, Crohn's disease, endometriosis, congestive heart failure, viral meningitis, cerebral infarction,

neuropathy, Kawasaki disease and sepsis (see, for example, Rovin, B. H. et al., Am. J. Kidney. Dis., 1998, 31, 1065; Lloyd, C. et al., Curr. Opin. Nephrol. Hypertens., 1998, 7, 281; Conti, P. et al., Allergy and Asthma Proc., 1998, 19, 121; Ransohoff, R. M. et al., Trends Neuroscience., 1998, 21, 154; and MacDermott, R. P. et al., Inflammatory Bowel Diseases, 1998, 4, 54). A drug which inhibits actions of chemokines on target cells, therefore, can be expected to be

useful as remedies and/or prophylactics for the diseases.

[0013] On the other hand, the cloning of genes encoding specific receptors for chemokines has been promoted, and it has become apparent that the receptors are G protein-coupled seven-transmembrane receptors present on various leukocytes. At least 5 CXC chemokine receptors (CXCR1 to CXCR5) and eight CC chemokine receptors (CCR1 to CCR8) have hitherto been specified. For example, IL-8 is a ligand of CXCR1 and CXCR2. MIP-1 α is a ligand of CCR1 and CCR5, and MCP-1 is a ligand of CCR2A and CCR2B (see, for example, Holmes, W. E. et al., Science, 1991, 253, 1278-1280; Murphy, P. M. et al., Science, 253, 1280-1283; Neote, K. et al., Cell, 1993, 72, 415-425; Charo, I. F. et al., Proc. Natl. Acad. Sci., USA, 1994, 91, 2752-2756; Yamagami, S. et al., Biochem. Biophys. Res. Commun., 1994, 202, 1156-1162; Combadier, C. et al., The Journal of Biological Chemistry, 1995, 270, 16491-16494; Power, C. A. et al., J. Biol. Chem., 1995, 270, 19495-19500; Samson, M. et al., Biochemistry, 1996, 35, 3362-3367; and Murphy, P. M. et al., Annual Review of Immunology, 1994, 12, 592-633).

[0014] Further, it has been reported that the pulmonary inflammation and granuloma are suppressed in CCR1 gene deficient mice (see, for example, Gao, J.-L. et al., J. Exp. Med., 1997, 185, 1959 and Gerard, C. et al., J. Clin. Invest., 1997, 100, 2022) and that accumulation of macrophages and formation of atherosclerotic lesions are decreased in CCR2 gene deficient mice (see, for example, Boring, L. et al., Nature, 1998, 394, 894; Kuziel, W. A. et al., Proc. Natl. Acad. Sci. USA, 1997, 94, 12053; Kurihara, T. et al., J. Exp. Med., 1997, 186, 1757; and Boring, L. et al., J. Clin. Invest., 1997, 100, 2552). Therefore, compounds capable of inhibiting binding of chemokines such as MIP-1 α and/or MCP-1 to the receptors, i.e. chemokine receptor antagonists can be expected to be useful as a drug which inhibits the actions of the chemokines such as MIP-1 α and/or MCP-1 on target cells; however, the drug having the actions is not known.

[0015] Cyclic amine derivatives such as various kinds of piperidines or piperazines have recently been reported to have chemokine receptor antagonistic activity (see, for example, WO9724325; Hesselgesser, J. et al., J. Biol. Chem., 1998, 273, 15687; Howard, O. M. Z. et al., J. Med. Chem., 1998, 41, 2184; WO9744329; WO9802151; WO9804554; WO9825605; WO9825617; WO9825604; WO9831364; WO9856771; WO9909984; WO9904794; WO9917773; WO9937617; WO9937619; WO9737651; WO9938514; WO200014086; WO200014089; EP903349; JP9-249566; JP9-25572; and JP11-711350). The compounds, however, are different from the compounds used in the present invention.

[0016] WO 99/25686 discloses cyclic amine derivatives that inhibit the action of chemokines such as MIP-1 α and MCP-1 on target cells.

[0017] WO 00/69815 discloses ureido-substituted cyclic amine derivatives that inhibit the action of chemokines such as MIP-1 α and MCP-1 on target cells.

[0018] Burzynski *et al.*, (1987), Drugs Exptl. Clin. Res., Suppl. 1, 57-60 discloses N,N'-disubstituted L-isoglutamines as novel cancer chemotherapeutic agents.

[0019] WO 98/50534 discloses cyclic amine derivatives that inhibit cysteine proteases, particularly cathepsin K, and are said to be useful in the treatment of diseases in which inhibition of bone loss is a factor.

[0020] EP-A-0217286 discloses phenylalanine derivatives that inhibit proteinases, for example the proteinase plasmin.

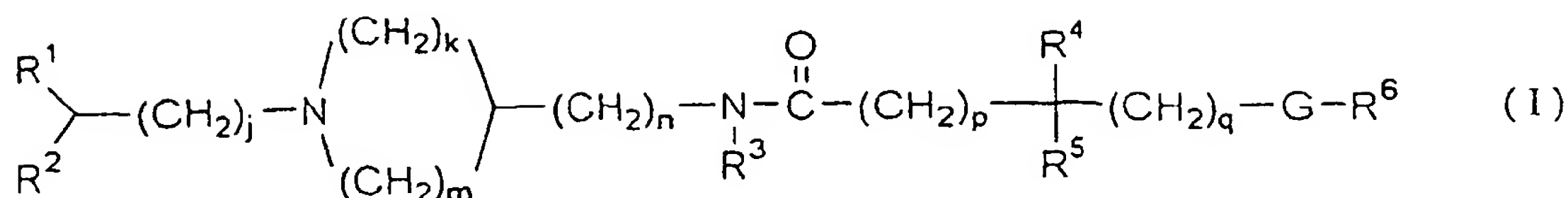
[0021] WO 00/31032 discloses pyrrolidine derivatives that are receptor CCR-3 antagonists.

Disclosure of the Invention

[0022] It is an object of the present invention to provide therapies for diseases wherein the binding of chemokines such as MIP-1 α and/or MCP-1 to receptors on target cells is one of the pathogenesis by using a small-molecular compound having an inhibitory activity against the binding of the chemokines such as MIP-1 α and/or MCP-1 to the receptors on the target cells.

[0023] As a result of intensive studies, the present inventors have found that cyclic amine derivatives having an arylalkyl group, pharmaceutically acceptable C₁-C₆ alkyl- addition salts thereof or pharmaceutically acceptable acid-addition salts thereof have an inhibitory activity against the binding of chemokines such as MIP-1 α and/or MCP-1 to the target cells and that the compounds can be useful as remedies or prophylactics for diseases considered to be associated with the chemokines such as MIP-1 α and/or MCP-1. The present invention has been accomplished on the basis of the findings.

[0024] That is, the present invention provides the use of a compound according to formula (I), or a pharmaceutically acceptable acid addition salt thereof or pharmaceutically acceptable C₁-C₆ alkyl addition salt thereof, in the manufacture of a medicament for the treatment of glomerulonephritis, interstitial nephritis or nephrotic syndrome.



wherein R¹ is a phenyl group, a C₃-C₈ cycloalkyl group or an aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms; the phenyl group or the aromatic heterocyclic group in the R¹ may be condensed with a benzene ring or an aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms to form a condensed ring; the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic group or the condensed ring in the above R¹ may be substituted with an optional number of halogen atoms, hydroxy groups, cyano groups, nitro groups, carboxy groups, carbamoyl groups, C₁-C₆ alkyl groups, C₃-C₈ cycloalkyl groups, C₂-C₆ alkenyl groups, C₁-C₆ alkoxy groups, C₁-C₆ alkylthio groups, C₃-C₅ alkylene groups, C₂-C₄ alkyleneoxy groups, C₁-C₃ alkylendioxy groups, phenyl groups, phenoxy groups, phenylthio groups, benzyl groups, benzyloxy groups, benzoylamino groups, C₂-C₇ alkanoyl groups, C₂-C₇ alkoxycarbonyl groups, C₂-C₇ alkanoyloxy groups, C₂-C₇ alkanoylamino groups, C₂-C₇ N-alkylcarbamoyl groups, C₄-C₉ N-cycloalkylcarbamoyl groups, C₁-C₆ alkylsulfonyl groups, C₃-C₈ (alkoxycarbonyl)methyl groups, N-phenylcarbamoyl groups, piperidinocarbonyl groups, morpholinocarbonyl groups, 1-pyrrolidinylcarbonyl groups, bivalent groups represented by the formula: -NH(C=O)O-, bivalent groups represented by the formula: -NH(C=S)O-, amino groups, mono(C₁-C₆ alkyl)amino groups or di(C₁-C₆ alkyl)amino groups; the substituent groups of the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic group or the condensed ring may further be substituted with an optional number of halogen atoms, hydroxy groups, amino groups, trifluoromethyl groups, C₁-C₆ alkyl groups or C₁-C₆ alkoxy groups;

R² is a hydrogen atom, a C₁-C₆ alkyl group, a C₂-C₇ alkoxycarbonyl group, hydroxy group or a phenyl group; the C₁-C₆ alkyl group or the phenyl group in the R² may be substituted with an optional number of halogen atoms, hydroxy groups, C₁-C₆ alkyl groups or C₁-C₆ alkoxy groups, with the proviso that R² is not hydroxy group when j is 0;

j is an integer of 0 to 2;

k is an integer of 0 to 2;

m is an integer of 2 to 4;

n is 0 or 1;

R³ is a hydrogen atom or a C₁-C₆ alkyl group (which may be substituted with one or two phenyl groups which may respectively be substituted with an optional number of the same or different halogen atoms, hydroxy groups, C₁-C₆ alkyl groups or C₁-C₆ alkoxy groups);

R⁴ and R⁵ are the same or different and are each a hydrogen atom, a hydroxy group, a phenyl group or a C₁-C₆ alkyl group; the C₁-C₆ alkyl group in the R⁴ and R⁵ may be substituted with an optional number of halogen atoms, hydroxy groups, cyano groups, nitro groups, carboxy groups, carbamoyl groups, mercapto groups, guanidino groups, C₃-C₈ cycloalkyl groups, C₁-C₆ alkoxy groups, C₁-C₆ alkylthio groups, phenyl groups (which may be substituted with an optional number of halogen atoms, hydroxy groups, C₁-C₆ alkyl groups, C₁-C₆ alkoxy groups or benzyloxy groups), phenoxy groups, benzyloxy groups, benzyloxycarbonyl groups, C₂-C₇ alkanoyl groups, C₂-C₇ alkoxycarbonyl groups, C₂-C₇ alkanoyloxy groups, C₂-C₇ alkanoylamino groups, C₂-C₇ N-alkylcarbamoyl groups, C₁-C₆ alkylsulfonyl groups, amino groups, mono(C₁-C₆ alkyl)amino groups, di(C₁-C₆ alkyl)amino groups or aromatic heterocyclic groups (having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms) or condensed rings formed by condensation of the aromatic heterocyclic groups (having the 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as the heteroatoms) with benzene rings or both R⁴ and R⁵ together may form a 3- to a 6-membered cyclic hydrocarbon;

p is 0 or 1;

q is 0 or 1;

G is a group represented by -CO-, -SO₂-, -CO-O-, -NR⁷-CO-, -CO-NR⁷-, -NH-CO-NH-, -NH-CS-NH-, -NR⁷-SO₂-, -SO₂-NR⁷-, -NH-CO-O- or -O-CO-NH-,

wherein R⁷ is a hydrogen atom or a C₁-C₆ alkyl group or R⁷, together with R⁵, may form a C₂-C₅ alkylene group;

R⁶ is a phenyl group, a C₃-C₈ cycloalkyl group, a C₃-C₆ cycloalkenyl group, a benzyl group or an aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms; the phenyl group, the benzyl group or the aromatic heterocyclic group in the R⁶ may be condensed with a benzene ring or an aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms to form a condensed ring; the phenyl group, the C₃-C₈ cycloalkyl group, the C₃-C₆ cycloalkenyl group, the benzyl group, the aromatic heterocyclic group or the condensed ring in the above R⁶ may further be substituted with an optional number of halogen atoms, hydroxy groups, mercapto groups, cyano groups, nitro groups, thiocyanato groups, carboxy groups, carbamoyl groups, trifluoromethyl groups, C₁-C₆ alkyl groups, C₃-C₈ cycloalkyl groups, C₂-C₆ alkenyl groups, C₁-C₆ alkoxy groups, C₃-C₈ cycloalkyloxy groups, C₁-C₆ alkylthio groups, C₁-C₃ alkylendioxy groups, phenyl groups, phenoxy

groups, phenylamino groups, benzyl groups, benzoyl groups, phenylsulfinyl groups, phenylsulfonyl groups, 3-phenylureido groups, C₂-C₇ alkanoyl groups, C₂-C₇ alkoxycarbonyl groups, C₂-C₇ alkanoyloxy groups, C₂-C₇ alkanoylamino groups, C₂-C₇ N-alkylcarbamoyl groups, C₁-C₆ alkylsulfonyl groups, phenylcarbamoyl groups, N,N-di(C₁-C₆ alkyl)sulfamoyl groups, amino groups, mono(C₁-C₆ alkyl)amino groups, di(C₁-C₆ alkyl)amino groups, benzylamino groups, C₂-C₇ (alkoxycarbonyl)amino groups, C₁-C₆ (alkylsulfonyl)amino groups or bis(C₁-C₆ alkylsulfonyl)amino groups; the substituent groups of the phenyl group, the C₃-C₈ cycloalkyl group, the C₃-C₈ cycloalkenyl group, the benzyl group, the aromatic heterocyclic group or the condensed ring may further be substituted with an optional number of halogen atoms, cyano groups, hydroxy groups, amino groups, trifluoromethyl groups, C₁-C₆ alkyl groups, C₁-C₆ alkoxy groups, C₁-C₆ alkylthio groups, mono(C₁-C₆ alkyl)amino groups or di(C₁-C₆ alkyl)amino groups.

[0025] The compounds represented by the above formula (I) have an inhibitory activity against the binding of chemokines such as MIP-1 α and/or MCP-1 to target cells and an inhibitory activity against physiological actions of the chemokines such as MIP-1 α and/or MCP-1 on the target cells.

Brief Description of Drawings

[0026]

Fig. 1 is a drawing illustrating effects of Compd. No. 1583 on arthritis when the compound is orally administered for 12 weeks.

Fig. 2 is a drawing illustrating effects of the Compd. No. 1583 on synovial hyperplasia.

Fig. 3 is a drawing illustrating effects of the Compd. No. 1583 on the chondrolysis of articular cartilages.

Fig. 4 is a drawing illustrating effects of the Compd. No. 1583 on the osteolysis of subchondral bone.

Fig. 5 is a drawing illustrating effects of Compd. No. 1245 on hindlimb footpads swelling when the compound is orally administered for 3 weeks.

Fig. 6 is a drawing illustrating suppressive effects of the Compd. No. 1583 on proteinuria.

Fig. 7 is a drawing illustrating suppressive effects of the Compd. No. 1245 on proteinuria.

Fig. 8 is a drawing illustrating effects of the Compd. No. 1583 in animal models of chronic relapsing experimental allergic encephalomyelitis.

Fig. 9 is a drawing illustrating effects of the Compd. No. 1245 in animal models of chronic relapsing experimental allergic encephalomyelitis.

Best Mode for Carrying Out the Invention

[0027] In the above formula (I), R¹ is a phenyl group, a C₃-C₈ cycloalkyl group or an aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms; the phenyl group or the aromatic heterocyclic group in the above R¹ may be condensed with a benzene ring or an aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms to form a condensed ring; the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic group or the condensed ring in the above R¹ may further be substituted with an optional number of halogen atoms, hydroxy groups, cyano groups, nitro groups, carboxy groups, carbamoyl groups, C₁-C₆ alkyl groups, C₃-C₈ cycloalkyl groups, C₂-C₆ alkenyl groups, C₁-C₆ alkoxy groups, C₁-C₆ alkylthio groups, C₃-C₅ alkylene groups, C₂-C₄ alkyleneoxy groups, C₁-C₃ alkylenedioxy groups, phenyl groups, phenoxy groups, phenylthio groups, benzyl groups, benzyloxy groups, benzoylamino groups, C₂-C₇ alkanoyl groups, C₂-C₇ alkoxycarbonyl groups, C₂-C₇ alkanoyloxy groups, C₂-C₇ alkanoylamino groups, C₂-C₇ N-alkylcarbamoyl groups, C₄-C₉ N-cycloalkylcarbamoyl groups, C₁-C₆ alkylsulfonyl groups, C₃-C₈ (alkoxycarbonyl)methyl groups, N-phenylcarbamoyl groups, piperidinocarbonyl groups, morpholinocarbonyl groups, 1-pyrrolidinyl carbonyl groups, bivalent groups represented by the formula -NH(C=O)O-, bivalent groups represented by the formula -NH(C=S)O-, amino groups, mono(C₁-C₆ alkyl)amino groups or di(C₁-C₆ alkyl)amino groups.

[0028] The "C₃-C₈ cycloalkyl group" in R¹ means a cyclic alkyl group, and includes for example cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group and the like. The "C₃-C₈ cycloalkyl group" is preferably cyclopropyl group, cyclopentyl group, cyclohexyl group or the like.

[0029] The "aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms" in R¹ means an aromatic heterocyclic group, and includes for example thienyl group, furyl group, pyrrolyl group, imidazolyl group, pyrazolyl group, oxazolyl group, isoxazolyl group, thiazolyl group, isothiazolyl group, pyridyl group, pyrimidinyl group, triazinyl group, triazolyl group, oxadiazolyl (furazanyl) group, thiadiazolyl group and the like. The "aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms" is preferably thienyl group, furyl group, pyrrolyl group, isoxazolyl group, pyridyl group or the like.

[0030] The "condensed ring" in R¹ means a bicyclic aromatic heterocyclic group formed by condensing the phenyl group or the aromatic heterocyclic group with a benzene ring or the aromatic heterocyclic group having 1 to 3 oxygen

atoms, sulfur atoms and/or nitrogen atoms as heteroatoms in an optional position, and includes for example naphthyl group, indolyl group, benzofuranyl group, benzothienyl group, quinolyl group, benzimidazolyl group, benzoxazolyl group, benzotriazolyl group, benzoxadiazolyl (benzofurazanyl) group, benzothiadiazolyl group and the like.

[0031] Among them, it is especially preferable for R¹ to be a phenyl group, an isoxazolyl group or an indolyl group.

[0032] The "halogen atoms" as the substituents of the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic group or the condensed ring mean a fluorine atom, a chlorine atom, a bromine atom, an iodine atom and the like, and fluorine atom, chlorine atom or bromine atom is specifically preferable.

[0033] The "C₁-C₆ alkyl groups" as the substituents of R¹ mean C₁-C₆ straight or branched alkyl groups, and include for example, methyl group, ethyl group, n-propyl group, n-butyl group, n-pentyl group, n-hexyl group, n-heptyl group, n-octyl group, isopropyl group, isobutyl group, sec-butyl group, tert-butyl group, isopentyl group, neopentyl group, tert-pentyl group, isohexyl group, 2-methylpentyl group, 1-ethylbutyl group and the like. The "C₁-C₆ alkyl groups" are specifically preferably methyl group, ethyl group, propyl group, isopropyl group or the like.

[0034] The "C₃-C₈ cycloalkyl groups" as the substituents of R¹ are the same as defined in the "C₃-C₈ cycloalkyl group" in the above R¹, and specifically preferably include for example the same groups.

[0035] The "C₂-C₆ alkenyl groups" as the substituents of R¹ mean C₂-C₆ straight or branched alkenyl groups, and include for example vinyl group, allyl group, 1-propenyl group, 2-butenyl group, 3-butenyl group, 2-methyl-1-propenyl group, 4-pentenyl group, 5-hexenyl group, 4-methyl-3-pentenyl group and the like. The "C₂-C₆ alkenyl groups" are specifically preferably vinyl group and 2-methyl-1-propenyl group or the like.

[0036] The "C₁-C₆ alkoxy groups" as the substituents of R¹ mean groups composed of the above C₁-C₆ alkyl groups and oxy group, and methoxy group, ethoxy group or the like is specifically preferable.

[0037] The "C₁-C₆ alkylthio groups" as the substituents of R¹ mean groups composed of the above C₁-C₆ alkyl groups and thio group, and methylthio group, ethylthio group or the like is specifically preferable.

[0038] The "C₃-C₅ alkylene groups" as the substituents of R¹ mean C₃-C₅ bivalent alkylene groups, and include for example, trimethylene group, tetramethylene group, pentamethylene group, 1-methyltrimethylene group and the like.

The "C₃-C₅ alkylene groups" are specifically preferably trimethylene group, tetramethylene group or the like.

[0039] The "C₂-C₄ alkyleneoxy groups" as the substituents of R¹ mean groups composed of C₂-C₄ bivalent alkylene groups and oxy group and include, for example, ethyleneoxy group (-CH₂CH₂O-), trimethyleneoxy group (-CH₂CH₂CH₂O-), tetramethyleneoxy group (-CH₂CH₂CH₂CH₂O-), 1,1-dimethylethyleneoxy group (-CH₂C(CH₃)₂O-) and the like. The "C₂-C₄ alkyleneoxy groups" are specifically preferably ethyleneoxy group, trimethyleneoxy group or the like.

[0040] The "C₁-C₃ alkylenedioxy groups" as the substituents of R¹ mean groups composed of C₁-C₃ bivalent alkylene groups and two oxy groups and include, for example, methylenedioxy group (-OCH₂O-), ethylenedioxy group (-OCH₂CH₂O-), trimethylenedioxy (-OCH₂CH₂CH₂O-) group and propylenedioxy (-OCH₂CH(CH₃)O-) group and the like. The "C₁-C₃ alkylenedioxy groups" are specifically preferably methylenedioxy group, ethylenedioxy group or the like.

[0041] The "C₂-C₇ alkanoyl groups" as the substituents of R¹ mean C₂-C₇ straight or branched alkanoyl groups, and include for example, acetyl group, propanoyl group, butanoyl group, pentanoyl group, hexanoyl group, heptanoyl group, isobutyryl group, 3-methylbutanoyl group, 2-methylbutanoyl group, pivaloyl group, 4-methylpentanoyl group, 3,3-dimethylbutanoyl group, 5-methylhexanoyl group and the like, and acetyl group or the like is specifically preferable.

[0042] The "C₂-C₇ alkoxycarbonyl groups" as the substituents of R¹ mean groups composed of the above C₁-C₆ alkoxy groups and carbonyl group, and methoxycarbonyl group, ethoxycarbonyl group or the like is specifically preferable.

[0043] The "C₂-C₇ alkanoyloxy groups" as the substituents of R¹ mean groups composed of the above C₂-C₇ alkanoyl groups and oxy group, and acetyloxy group or the like is specifically preferable.

[0044] The "C₂-C₇ alkanoylamino groups" as the substituents of R¹ mean groups composed of the above C₂-C₇ alkanoyl groups and amino group, and acetylamino group or the like is specifically preferable.

[0045] The "C₂-C₇ alkylcarbamoyl groups" as the substituents of R¹ mean groups composed of the above C₁-C₆ alkyl groups and carbamoyl group, and N-methylcarbamoyl group, N-ethylcarbamoyl group or the like is specifically preferable.

[0046] The "C₄-C₉ N-cycloalkylcarbamoyl groups" as the substituents of R¹ mean the above C₃-C₈ cycloalkyl groups and carbamoyl group, and N-cyclopentylcarbamoyl group, N-cyclohexylcarbamoyl group or the like is preferable.

[0047] The "C₁-C₆ alkylsulfonyl groups" as the substituents of R¹ mean groups composed of the above C₁-C₆ alkyl groups and sulfonyl group, and methylsulfonyl group or the like is specifically preferable.

[0048] The "C₃-C₈ (alkoxycarbonyl)methyl groups" as the substituents of R¹ mean groups composed of the above C₂-C₇ alkoxycarbonyl groups and methyl group, and (methoxycarbonyl)methyl group, (ethoxycarbonyl)methyl group or the like is specifically preferable.

[0049] The "mono(C₁-C₆ alkyl)amino groups" as the substituents of R¹ mean amino groups substituted with the above C₁-C₆ alkyl groups, and methylamino group, ethylamino group or the like is specifically preferable.

[0050] The "di(C₁-C₆ alkyl)amino groups" as the substituents of R¹ mean amino groups substituted with the same

or different two C₁-C₆ alkyl groups described above, and dimethylamino group, diethylamino group, N-ethyl-N-methylamino group or the like is specifically preferable.

[0051] Among those described above, examples of the substituents of the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic group or the condensed ring in R¹ are specifically preferably halogen atoms, hydroxy groups, C₁-C₆ alkyl groups, C₂-C₆ alkenyl groups, C₁-C₆ alkoxy groups, C₁-C₆ alkylthio groups, C₂-C₄ alkyleneoxy groups, methylenedioxy groups, N-phenylcarbonyl groups, amino groups, mono(C₁-C₆ alkyl)amino groups and di(C₁-C₆ alkyl)amino groups.

[0052] Moreover, the substituents of the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic group or the condensed ring in R¹ may further be substituted with an optional number of halogen atoms, hydroxy groups, amino groups, trifluoromethyl groups, C₁-C₆ alkyl groups or C₁-C₆ alkoxy groups. The halogen atoms, C₁-C₆ alkyl groups and C₁-C₆ alkoxy groups are the same as defined for the substituents of the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic group or the condensed ring in R¹, and the same groups are specifically preferable.

[0053] In the above formula (I), R² is a hydrogen atom, a C₁-C₆ alkyl group, a C₂-C₇ alkoxy carbonyl group, a hydroxy group or a phenyl group; and the C₁-C₆ alkyl group or phenyl group in R² may be substituted with an optional number of halogen atoms, hydroxy groups, C₁-C₆ alkyl groups or C₁-C₆ alkoxy groups, with the proviso that R² is not a hydroxy group when j is 0.

[0054] The C₁-C₆ alkyl group and C₂-C₇ alkoxy carbonyl group in R² are each the same as defined for the substituents of the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic group or the condensed ring in R¹, and the same examples are specifically preferable.

[0055] The halogen atoms, C₁-C₆ alkyl groups and C₁-C₆ alkoxy groups as the substituents of the C₁-C₆ alkyl group or the phenyl group in R² are the same as defined for the substituents of the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic group or the condensed ring in the above R¹, and the same examples are specifically preferable.

[0056] Among them, it is especially preferable for R² to be a hydrogen atom.

[0057] In the above formula (I), j is an integer of 0 to 2, and it is especially preferable for j to be 0.

[0058] In the above formula (I), k is an integer of 0 to 2; m is an integer of 2 to 4. Among them, it is especially preferable for the compounds to be 2-substituted pyrrolidines wherein k is 0 and m is 3; 3-substituted pyrrolidines wherein k is 1 and m is 2; 3-substituted piperidines wherein k is 1 and m is 3; 4-substituted piperidines wherein k is 2 and m is 2; or 3-substituted hexahydroazepines wherein k is 1 and m is 4.

[0059] In the above formula (I), n is 0 or 1.

[0060] In particular, 3-amidopyrrolidines wherein k is 1; m is 2 and n is 0 and 4-(amidomethyl)piperidines wherein k is 2; m is 2 and n is 1 are especially preferable.

[0061] In the above formula (I), R³ is a hydrogen atom or a C₁-C₆ alkyl group which may be substituted with (one or two phenyl groups which may respectively be substituted with an optional number of the same or different halogen atoms, hydroxy groups, C₁-C₆ alkyl groups or C₁-C₆ alkoxy groups).

[0062] The C₁-C₆ alkyl group in R³ is the same as defined for the substituent group of the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic group or the condensed ring in the above R¹, and methyl group, ethyl group or propyl group is specifically preferable.

[0063] The halogen atoms, C₁-C₆ alkyl groups and C₁-C₆ alkoxy groups as the substituents of the phenyl groups as the substituents of the C₁-C₆ alkyl group in R³ are each the same as defined for substituents of the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic group or the condensed ring in the above R¹, and the same examples are specifically preferable.

[0064] Among them, it is especially preferable for R³ to be a hydrogen atom.

[0065] In the above formula (I), R⁴ and R⁵ are each the same or different and are each a hydrogen atom, a hydroxy group, a phenyl group or a C₁-C₆ alkyl group; and the C₁-C₆ alkyl group in R⁴ and R⁵ may be substituted with an optional number of halogen atoms, hydroxy groups, cyano groups, nitro groups, carboxy groups, carbonyl groups, mercapto groups, guanidino groups, C₃-C₈ cycloalkyl groups, C₁-C₆ alkoxy groups, C₁-C₆ alkylthio groups, (phenyl groups which may be substituted with an optional number of halogen atoms, hydroxy groups, C₁-C₆ alkyl groups, C₁-C₆ alkoxy groups or benzyloxy groups), phenoxy groups, benzyloxy groups, benzyloxycarbonyl groups, C₂-C₇ alkanoyl groups, C₂-C₇ alkoxy carbonyl groups, C₂-C₇ alkanoyloxy groups, C₂-C₇ alkanoylamino groups, C₂-C₇ N-alkyl carbonyl groups, C₁-C₆ alkylsulfonyl groups, amino groups, mono(C₁-C₆ alkyl)amino groups, di(C₁-C₆ alkyl)amino groups or (aromatic heterocyclic groups having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms or condensed rings formed by condensation thereof with benzene rings) or both R⁴ and R⁵ together may form a 3- to a 6-membered cyclic hydrocarbon.

[0066] The C₁-C₆ alkyl group in R⁴ and R⁵ is the same as defined for the substituents of the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic group or the condensed ring in the above R¹, and the same examples are specifically preferable.

[0067] The halogen atoms, C₁-C₆ alkoxy groups, C₁-C₆ alkylthio groups, C₂-C₇ alkanoyl groups, C₂-C₇ alkoxy car-

bonyl groups, C₂-C₇ alkanoyloxy groups, C₂-C₇ alkanoylamino groups, C₂-C₇ N-alkylcarbamoyl groups, C₁-C₆ alkylsulfonyl groups, mono(C₁-C₆ alkyl)amino groups and di(C₁-C₆ alkyl)amino groups as the substituents of the C₁-C₆ alkyl group in R⁴ and R⁵ are the same as defined for the substituents of the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic group or the condensed ring in the above R¹, and the same examples are specifically preferable.

[0068] The C₃-C₈ cycloalkyl groups and the aromatic heterocyclic groups having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms as the substituents of the C₁-C₆ alkyl group in R⁴ and R⁵ are the same as defined for the above R¹, and the same examples are preferable.

[0069] The halogen atoms, C₁-C₆ alkyl groups and C₁-C₆ alkoxy groups as the substituents of the phenyl groups as the substituents of the C₁-C₆ alkyl group in R⁴ and R⁵ are the same as defined for the substituents of the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic group or the condensed ring in the above R¹, and the same examples are specifically preferable.

[0070] The "3- to 6-membered cyclic hydrocarbon" composed of R⁴, R⁵ and the adjacent carbon atoms are specifically preferably cyclopropane, cyclobutane, cyclopentane, cyclohexane or the like.

[0071] Among them, the hydrogen atom and C₁-C₆ alkyl group are especially preferable for R⁴ and R⁵.

[0072] In the above formula (I), p is 0 or 1; and q is 0 or 1. Both p and q are especially preferably 0.

[0073] In the above formula (I), G is a group represented by -CO-, -SO₂-, -CO-O-, -NR⁷-CO-, -CO-NR⁷-, -NH-CO-NH-, -NH-CS-NH-, -NR⁷-SO₂-, -SO₂-NR⁷-, -NH-CO-O- or -O-CO-NH-,

wherein R⁷ is a hydrogen atom or a C₁-C₆ alkyl group or R⁷, together with R⁵, may form a C₂-C₅ alkylene group, wherein, -CO- is a carbonyl group, -SO₂- is a sulfonyl group and -CS- is a thiocarbonyl group. G is especially preferably the group represented by -NR⁷-CO- or -NH-CO-NH-.

[0074] The C₁-C₆ alkyl group in R⁷ is the same as defined for the substituents of the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic group or the condensed ring in the above R¹, and the same examples are specifically preferable.

[0075] The "C₂-C₅ alkylene group" composed of R⁵ and R⁷ means a C₂-C₅ straight or branched alkylene group, for example, methylene group, ethylene group, propylene group, trimethylene group, tetramethylene group, 1-methyltrimethylene group, pentamethylene group and the like, and ethylene group, trimethylene group, tetramethylene group or the like is specifically preferable.

[0076] Among them, it is especially preferable for R⁷ to be a hydrogen atom.

[0077] In the above formula (I), R⁶ is a phenyl group, a C₃-C₈ cycloalkyl group, a C₃-C₆ cycloalkenyl group, a benzyl group or an aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms; and the phenyl group, the benzyl group or the aromatic heterocyclic group in the above R⁶ may be condensed with a benzene ring or the aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms to form a condensed ring; and the phenyl group, the C₃-C₈ cycloalkyl group, the C₃-C₆ cycloalkenyl group, the benzyl group, the aromatic heterocyclic group or the condensed ring in the above R⁶ may be substituted with an optional number of halogen atoms, hydroxy groups, mercapto groups, cyano groups, nitro groups, thiocyanato groups, carboxy groups, carbamoyl groups, trifluoromethyl groups, C₁-C₆ alkyl groups, C₃-C₈ cycloalkyl groups, C₂-C₆ alkenyl groups, C₁-C₆ alkoxy groups, C₃-C₈ cycloalkyloxy groups, C₁-C₆ alkylthio groups, C₁-C₃ alkylenedioxy groups, phenyl groups, phenoxy groups, phenylamino groups, benzyl groups, benzoyl groups, phenylsulfinyl groups, phenylsulfonyl groups, 3-phenylureido groups, C₂-C₇ alkanoyl groups, C₂-C₇ alkoxycarbonyl groups, C₂-C₇ alkanoyloxy groups, C₂-C₇ alkanoylamino groups, C₂-C₇ N-alkylcarbamoyl groups, C₁-C₆ alkylsulfonyl groups, phenylcarbamoyl groups, N,N-di(C₁-C₆ alkyl)sulfamoyl groups, amino groups, mono(C₁-C₆ alkyl)amino groups, di(C₁-C₆ alkyl)amino groups, benzylamino groups, C₂-C₇ (alkoxycarbonyl)amino groups, C₁-C₆ (alkylsulfonyl)amino groups or bis(C₁-C₆ alkylsulfonyl)amino groups.

[0078] The C₃-C₈ cycloalkyl groups, aromatic heterocyclic groups having oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms, or condensed rings in R⁶ are the same as defined for the above R¹, and the same examples are specifically preferable.

[0079] The "C₃-C₈ cycloalkenyl groups" in R⁶ mean cycloalkenyl groups, for example, cyclobutenyl group, cyclopentenyl group, cyclohexenyl group, cycloheptenyl group and cyclooctenyl group, and 1-cyclopentenyl group, 1-cyclohexenyl group or the like is specifically preferable.

[0080] Among them, it is especially preferable for R⁶ to be a phenyl group, a furyl group and a theinyl group.

[0081] The halogen atoms, C₁-C₆ alkyl groups, C₁-C₆ alkenyl groups, C₁-C₆ alkoxy groups, C₁-C₆ alkylthio groups, C₁-C₃ alkylenedioxy groups, C₂-C₇ alkanoyl groups, C₂-C₇ alkoxycarbonyl groups, C₂-C₇ alkanoyloxy groups, C₂-C₇ alkanoylamino groups, C₂-C₇ N-alkylcarbamoyl groups, C₁-C₆ alkylsulfonyl groups, mono(C₁-C₆ alkyl)amino groups and di(C₁-C₆ alkyl)amino groups as the substituents of the phenyl group, the C₃-C₈ cycloalkyl group, the C₃-C₈ cycloalkenyl group, the benzyl group, the aromatic heterocyclic group or the condensed ring in R⁶ are the same as defined for the substituents of the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic group or the condensed ring in the above R¹, and the same examples are specifically preferable.

[0082] The C₃-C₈ cycloalkyl groups as the substituents of R⁶ are the same as defined for the C₃-C₈ cycloalkyl groups in the above R¹, and the same examples are specifically preferable.

[0083] The "C₃-C₈ cycloalkyloxy groups" as the substituents of R⁶ mean groups composed of the above C₃-C₈ cycloalkyl groups and oxy groups, and cyclopropyloxy group, cyclopentyloxy group, cyclohexyloxy group or the like is specifically preferable.

[0084] The "N,N-di(C₁-C₆ alkyl)sulfamoyl groups" as the substituents of R⁶ mean sulfamoyl groups substituted with the same or different two C₁-C₆ alkyl groups described above, and N,N-dimethylsulfamoyl group, N,N-diethylsulfamoyl group, N-ethyl-N-methylsulfamoyl group or the like is specifically preferable.

[0085] The "C₂-C₇ (alkoxycarbonyl)amino groups" as the substituents of R⁶ mean groups composed of the above C₂-C₇ alkoxycarbonyl groups and amino groups, and (methoxycarbonyl)amino group, (ethoxycarbonyl)amino group or the like is specifically preferable.

[0086] The "C₁-C₆ (alkylsulfonyl)amino groups" as the substituents of R⁶ mean groups composed of the above C₁-C₆ alkylsulfonyl groups and amino groups, and (methylsulfonyl)amino group or the like is specifically preferable.

[0087] The "bis(C₁-C₆ alkylsulfonyl)amino groups" as the substituents of R⁶ mean amino groups substituted with the same or different two C₁-C₆ alkylsulfonyl groups described above, and bis(methylsulfonyl)amino group or the like is specifically preferable.

[0088] Among them, halogen atoms, mercapto groups, nitro groups, thiocyanate groups, trifluoromethyl groups, C₁-C₆ alkyl groups, C₁-C₆ alkoxy groups, phenyl groups, phenylsulfonyl groups, C₂-C₇ alkanoylamino groups, amino groups and the like are especially preferable for the substituents of the phenyl groups, the C₃-C₈ cycloalkyl group, the C₃-C₈ cycloalkenyl group, the benzyl group, the aromatic heterocyclic group or the condensed group in R⁶.

[0089] The substituents of the phenyl group, the C₃-C₈ cycloalkyl group, the C₃-C₈ cycloalkenyl group, the benzyl group, the aromatic heterocyclic group or the condensed ring in such R⁶ may further be substituted with an optional number of halogen atoms, cyano groups, hydroxy groups, amino groups, trifluoromethyl groups, C₁-C₆ alkyl groups, C₁-C₆ alkoxy groups, C₁-C₆ alkylthio groups, mono(C₁-C₆ alkyl)amino groups or di(C₁-C₆ alkyl)amino groups.

[0090] The halogen atoms, C₁-C₆ alkyl groups, C₁-C₆ alkoxy groups, C₁-C₆ alkylthio groups, mono(C₁-C₆ alkyl)amino groups and di(C₁-C₆ alkyl)amino groups as the substituents of the phenyl group, the C₃-C₈ cycloalkyl group, the C₃-C₈ cycloalkenyl group, the benzyl group, the aromatic heterocyclic group or the condensed ring are the same as defined for the substituents of the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic aromatic group or the condensed ring in the above R¹, and the same examples are specifically preferable.

[0091] The remedially effective amount of the compounds represented by the above formula (I), pharmaceutically acceptable acid addition salts thereof or pharmaceutically acceptable C₁-C₆ alkyl-addition salts thereof together with a pharmaceutically acceptable carrier and/or a diluent can be prepared as a pharmaceutical composition and thus can be converted into medicines of the present invention capable of inhibiting the binding of chemokines to receptors on target cells, medicines having inhibitory actions on the binding of chemokines onto target cells or further remedies or prophylactics for diseases considered to be associated with chemokines or chemokine receptors. Namely, the cyclic amine derivatives represented by the above formula (I), pharmaceutically acceptable acid addition salts thereof or pharmaceutically acceptable C₁-C₆ alkyl addition salts thereof can be administered orally or parenterally such as intravenously, subcutaneously, intramuscularly, percutaneously or intrarectally.

[0092] For example, a tablet, a pill, a granule, a powder, a solution, a suspension or a capsule can be cited as the dosage form of the oral administration.

[0093] The tablet can be formed by using an vehicle, for example, lactose, starch or crystalline cellulose; a binder, for example, carboxymethylcellulose, methylcellulose or polyvinylpyrrolidone; or a disintegrator, for example, sodium alginate, sodium bicarbonate or sodium lauryl sulfate or the like according to a conventional method.

[0094] The pill, powder and granule can similarly be formed with using the above vehicle or the like according to a conventional method. The solution and suspension are produced with using glycerin esters, for example, tricaprillin or triacetin or alcohols, for example, ethanol according to a conventional method. The capsule is produced with filling a granule, powder or solution in a capsule such as gelatin.

[0095] A parenteral injection such as the form of an aqueous or a nonaqueous solution formulation is cited as the dosage form of subcutaneous, intramuscular or intravenous administration. For example, a isotonic sodium chloride solution is used as the aqueous solution. For example, propylene glycol, polyethylene glycol, olive oil or ethyl oleate is used for the nonaqueous solution. An antiseptic, a stabilizer or the like, if necessary, is added thereto. The parenteral injection is sterilized by suitably carrying out treatment such as filtration through a bacterial filter or combination of a disinfectant.

[0096] For example, an ointment or a cream is cited as the dosage form of percutaneous administration. The ointment is prepared by using oils and fats such as castor oil or olive oil or vaseline, and the cream is formed by using a fatty oil or an emulsifying agent such as diethylene glycol or sorbitan mono-fatty acid ester according to a conventional method.

[0097] A usual suppository such as a gelatin soft capsule is used for intrarectal administration.

[0098] The dose of the cyclic amine derivatives, pharmaceutically acceptable acid addition salts thereof or pharmaceutically acceptable C₁-C₆ alkyl addition salts thereof used in the present invention varies with the types of diseases, routes of administration, age and sex of patients and severity of diseases and the like, but is usually 1 to 500 mg/day for an adult.

[0099] Examples of the cyclic amine derivatives represented by the above formula (I) preferably include compounds having respective substituents shown in the following Tables 1.1 to 1.206

[0100] In Tables 1.1 to 1.206, "Table" means "Table", and "Compd. No." means "compound number". "Chirality" means the "absolute configuration", i.e. the absolute configuration of asymmetric carbon on the ring of the cyclic amine. "R" means that the asymmetric carbon atom on the ring of the cyclic amine has the absolute configuration of *R*, and "S" means that the asymmetric carbon atom has the absolute configuration of *S*. "-" means that the compound is a racemate or the compound has no asymmetric carbon atom on the cyclic amines.

Table 1.1

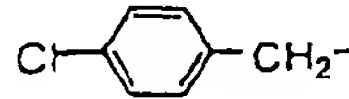
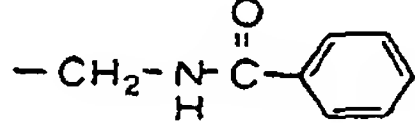
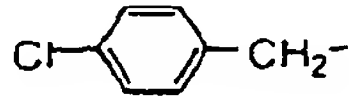
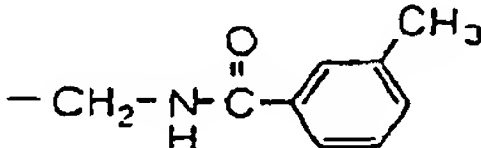
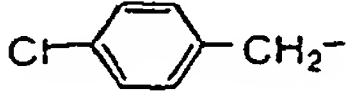
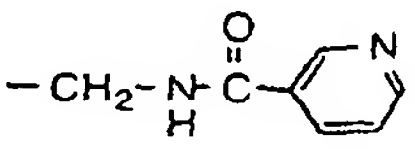
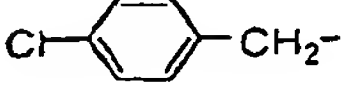
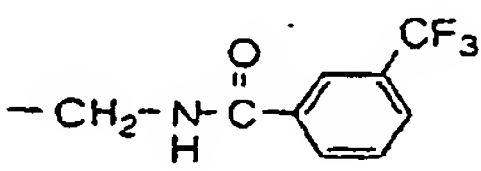
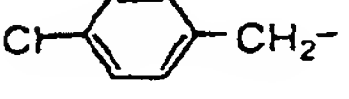
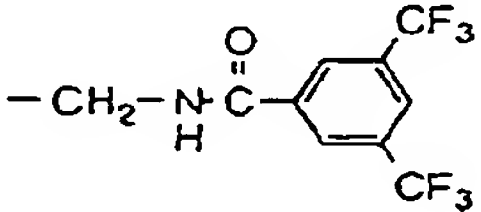
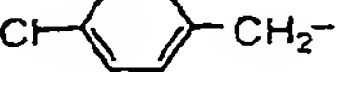
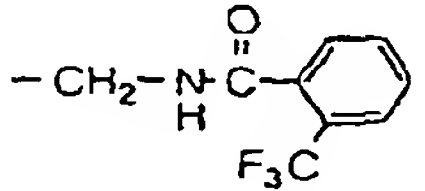
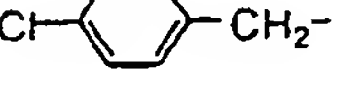
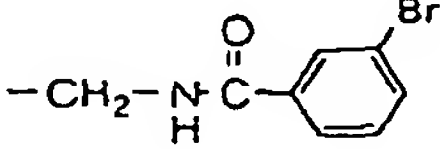

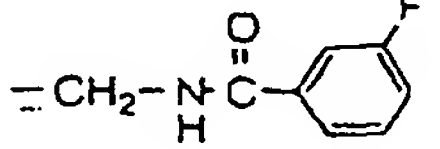

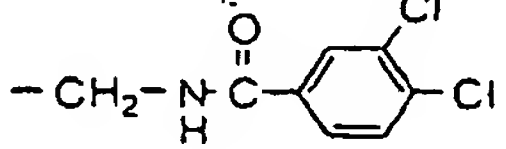
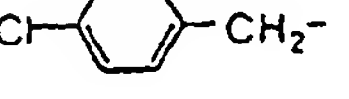
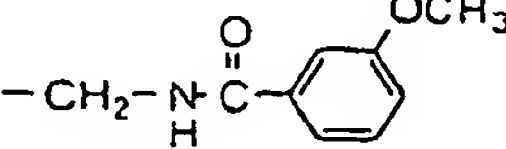
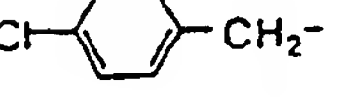
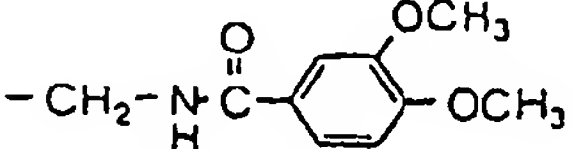
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2		1	2	0	-	H	
3		1	2	0	-	H	
4		1	2	0	-	H	
5		1	2	0	S	H	
6		1	2	0	S	H	
7		1	2	0	S	H	
8		1	2	0	S	H	
9		1	2	0	S	H	
10		1	2	0	S	H	
11		1	2	0	S	H	

Table 1.2

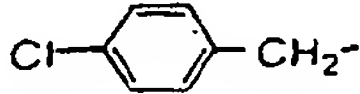
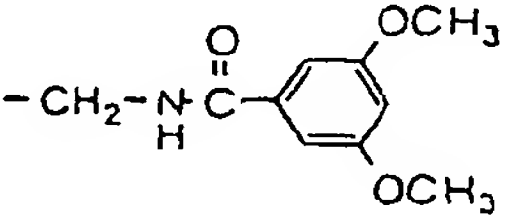
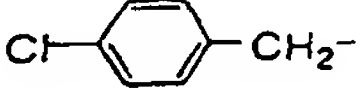
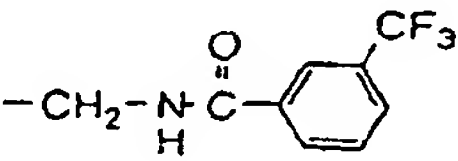
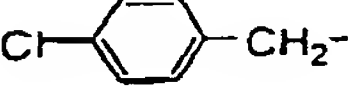
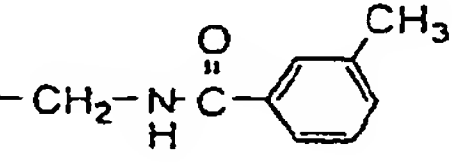
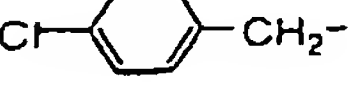
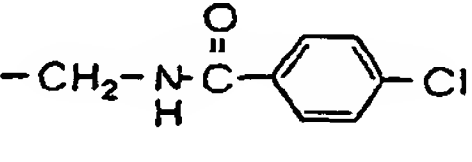
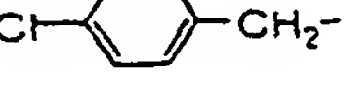
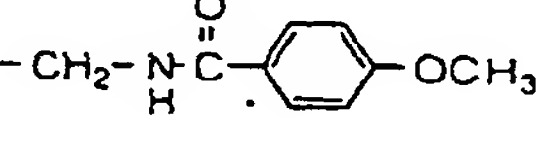
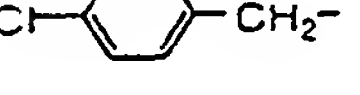
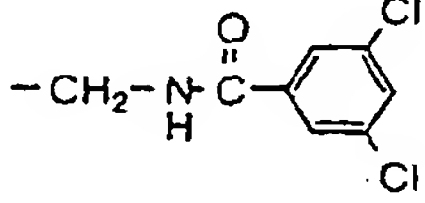

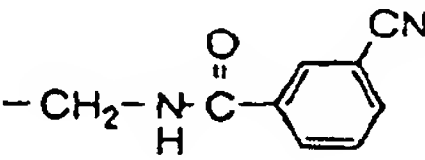

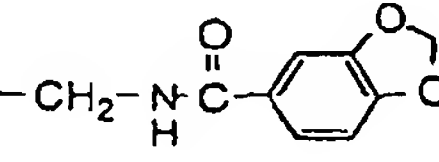

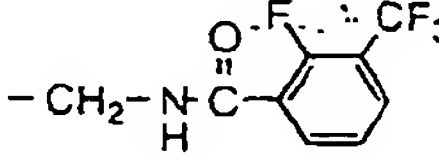

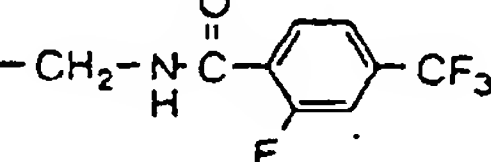
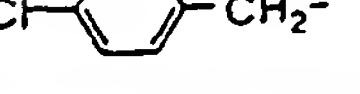
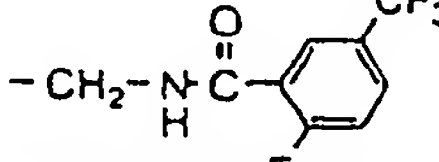
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13		1	2	0	S	H	
14		1	2	0	S	H	
15		1	2	0	S	H	
16		1	2	0	S	H	
17		1	2	0	S	H	
18		1	2	0	S	H	
19		1	2	0	S	H	
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21		1	2	0	S	H	
22		1	2	0	S	H	

Table 1.3

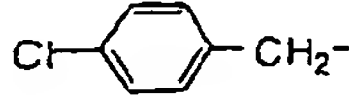
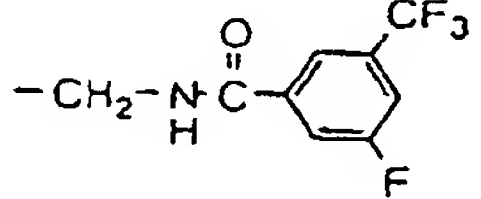
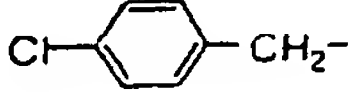
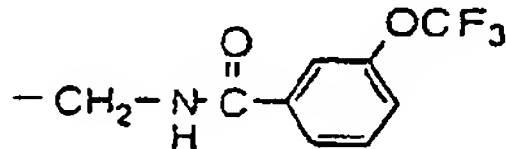
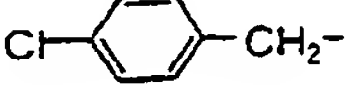
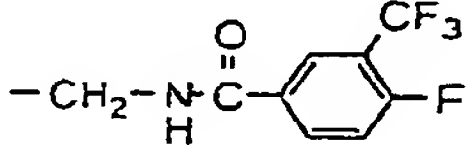
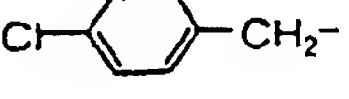
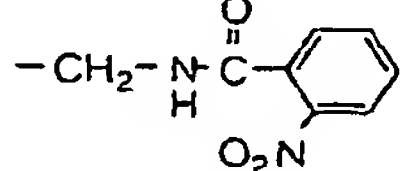
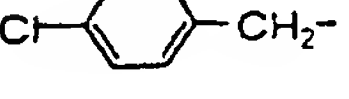
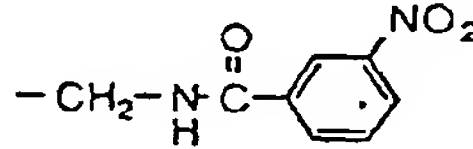
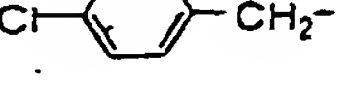
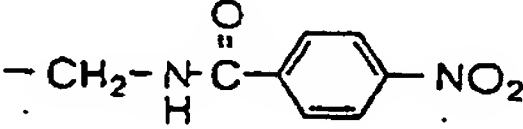
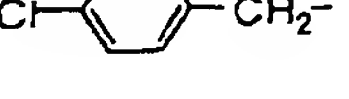
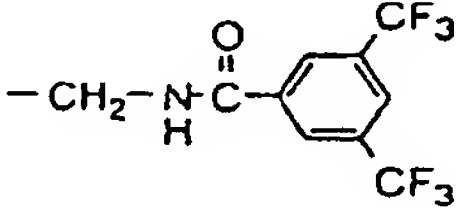

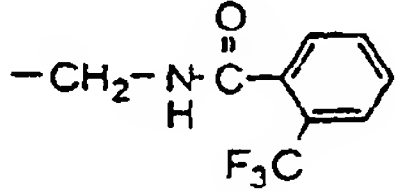

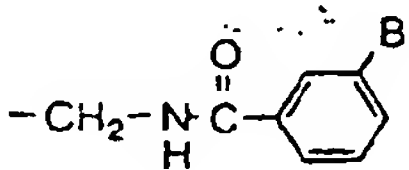

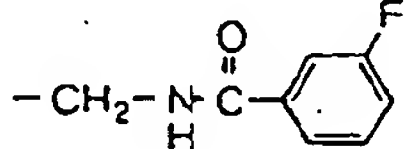
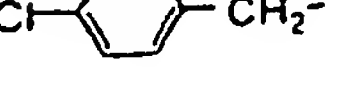
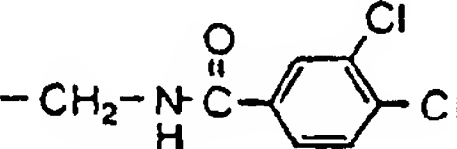
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24		1	2	0	S	H	
25		1	2	0	S	H	
26		1	2	0	S	H	
27		1	2	0	S	H	
28		1	2	0	S	H	
29		1	2	0	R	H	
30		1	2	0	R	H	
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33		1	2	0	R	H	

Table 1.4

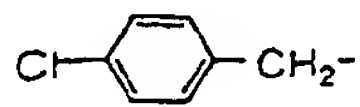
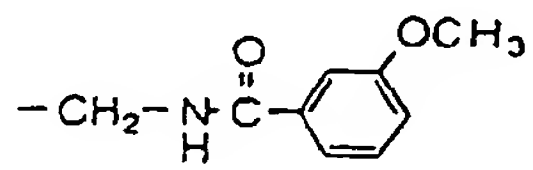
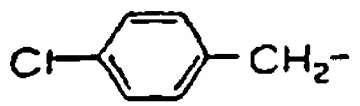
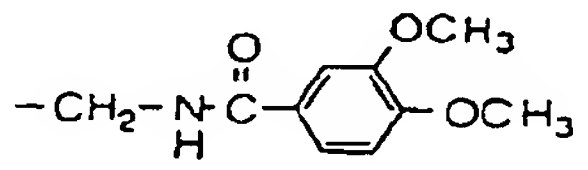
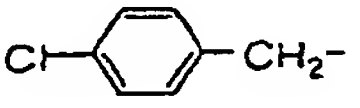
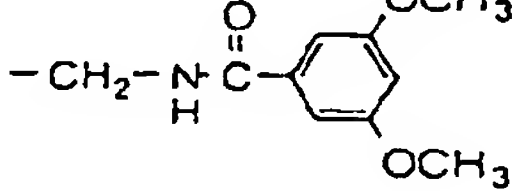
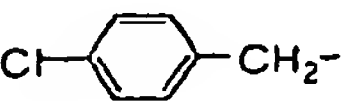
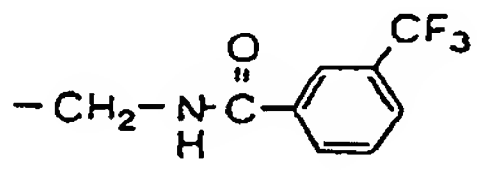
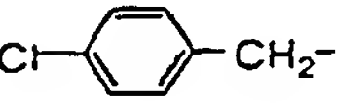
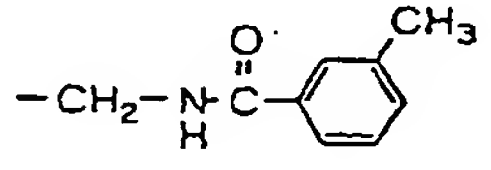
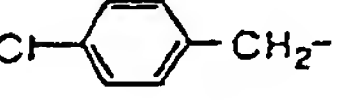
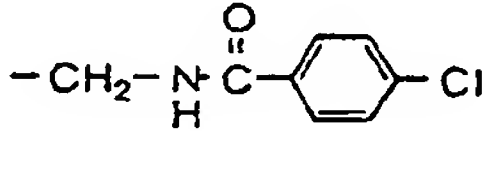
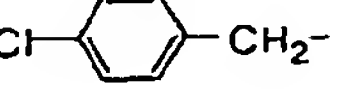
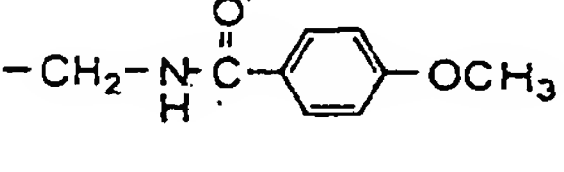
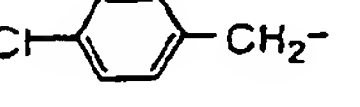
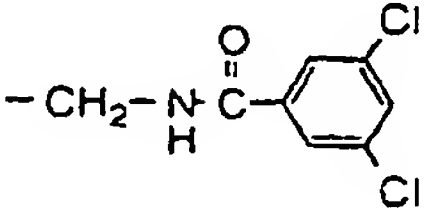
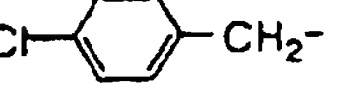
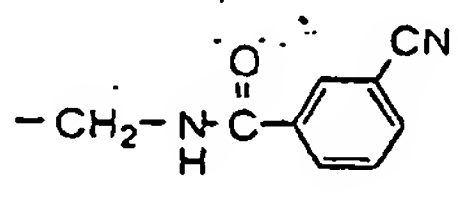
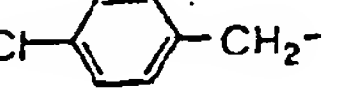
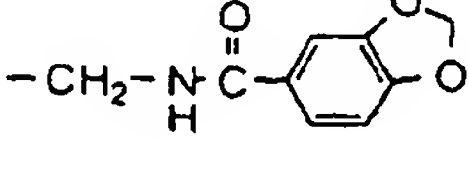
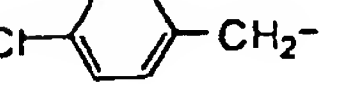
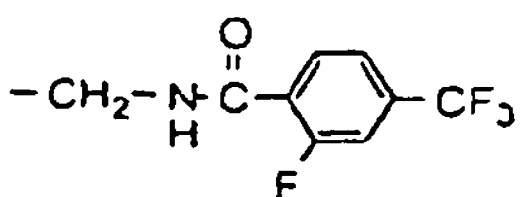
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_l \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
34		1	2	0	R	H	
35		1	2	0	R	H	
36		1	2	0	R	H	
37		1	2	0	R	H	
38		1	2	0	R	H	
39		1	2	0	R	H	
40		1	2	0	R	H	
41		1	2	0	R	H	
42		1	2	0	R	H	
43		1	2	0	R	H	
44		1	2	0	R	H	

Table 1.5


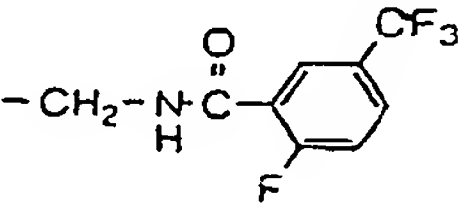
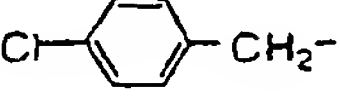
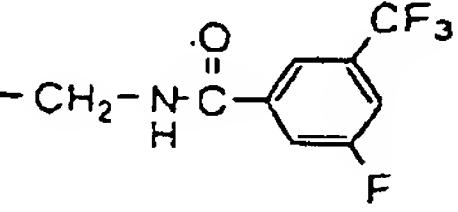

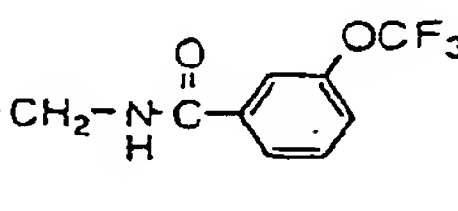
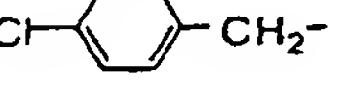
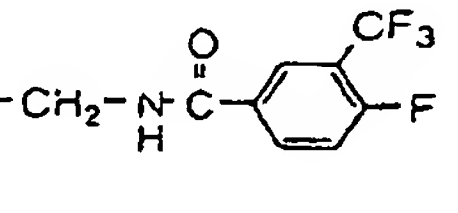
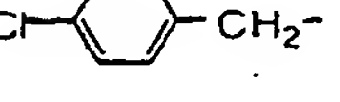
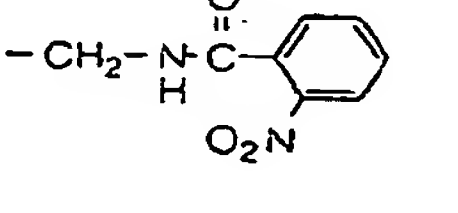
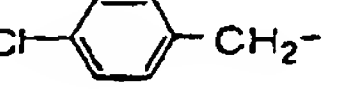
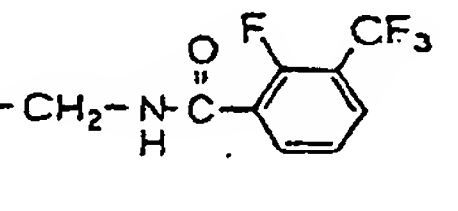
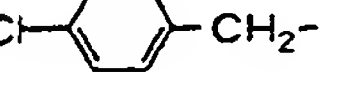
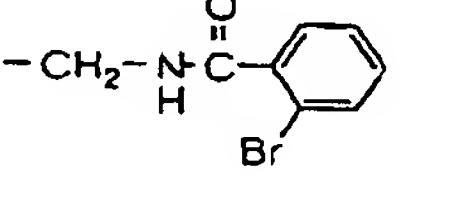
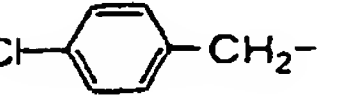
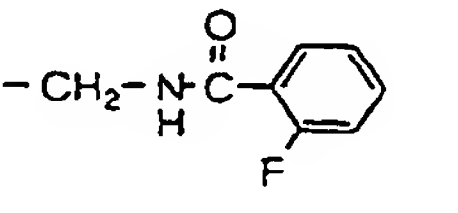
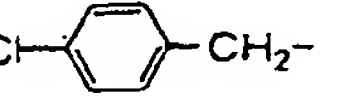
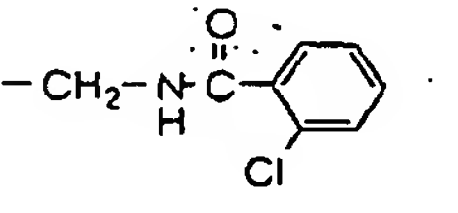
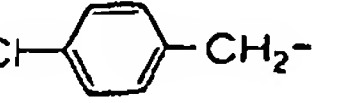
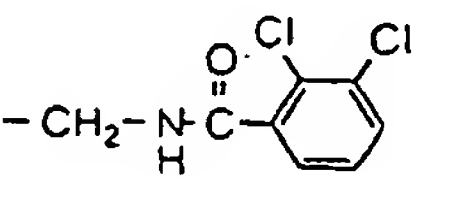
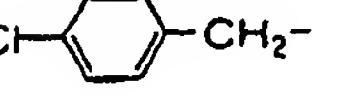
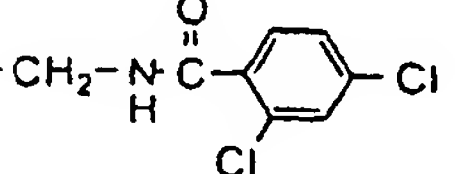
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_f \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
45		1	2	0	R	H	
46		1	2	0	R	H	
47		1	2	0	R	H	
48		1	2	0	R	H	
49		1	2	0	R	H	
50		1	2	0	R	H	
51		1	2	0	R	H	
52		1	2	0	R	H	
53		1	2	0	R	H	
54		1	2	0	R	H	
55		1	2	0	R	H	

Table 1.6

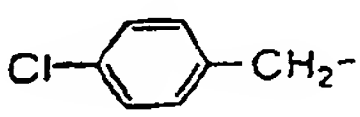
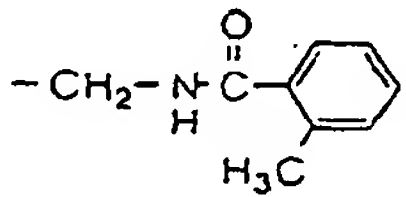
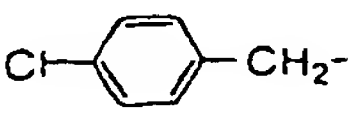
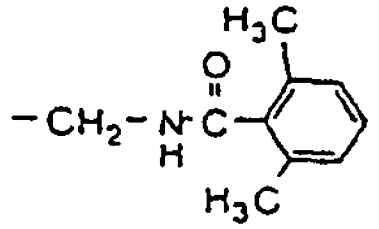
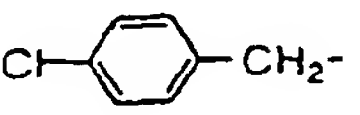
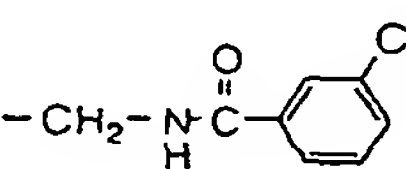
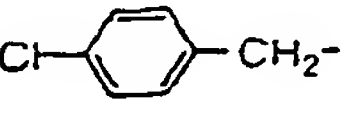
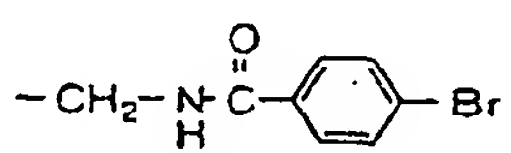
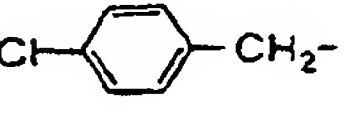
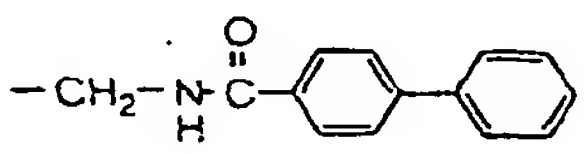
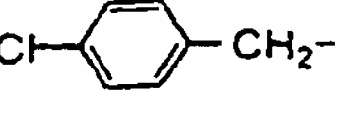
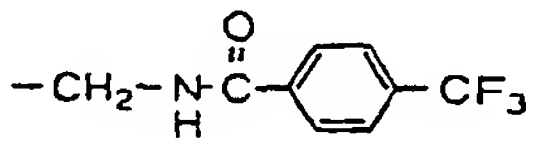
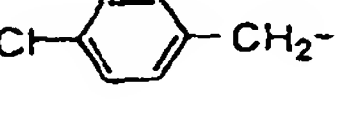
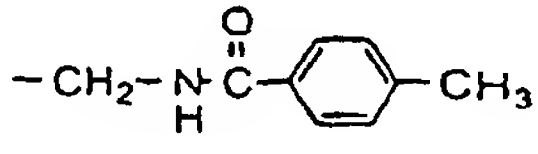
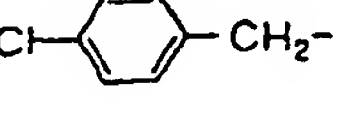
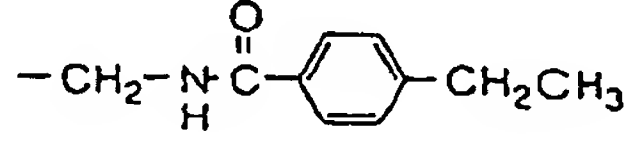
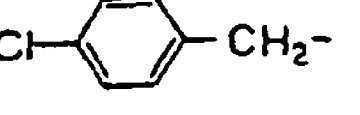
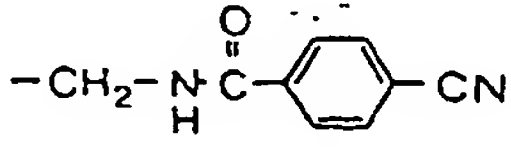
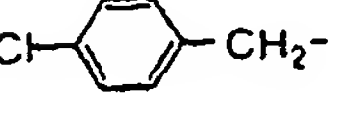
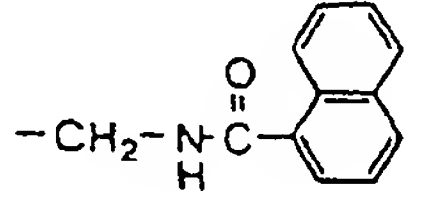
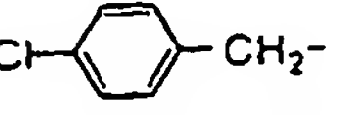
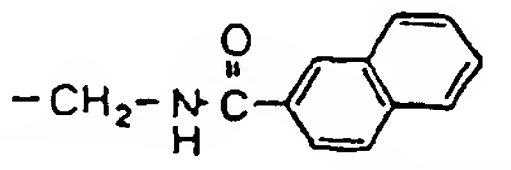
Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ (CH_2)_j- \\ \diagdown \\ R^2 \end{matrix}$	k	m	n	chirality	R^3	$-(CH_2)_p-\overset{\overset{R^4}{ }}{\underset{\underset{R^5}{ }}{C}}-(CH_2)_q-G-R^6$
56		1	2	0	R	H	
57		1	2	0	R	H	
58		1	2	0	R	H	
59		1	2	0	R	H	
60		1	2	0	R	H	
61		1	2	0	R	H	
62		1	2	0	R	H	
63		1	2	0	R	H	
64		1	2	0	R	H	
65		1	2	0	R	H	
66		1	2	0	R	H	

Table 1.7

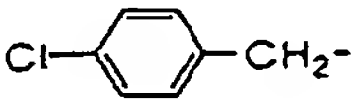
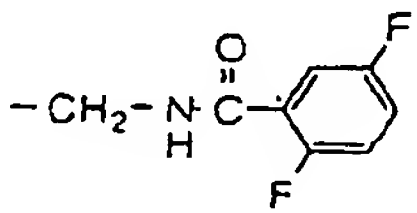
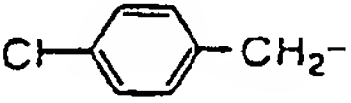
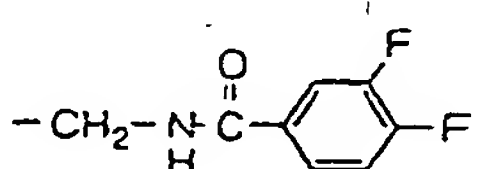

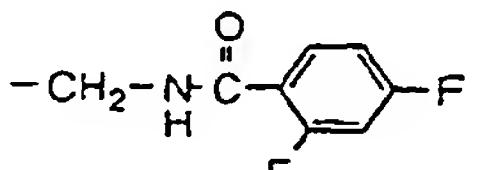
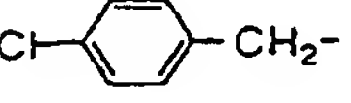
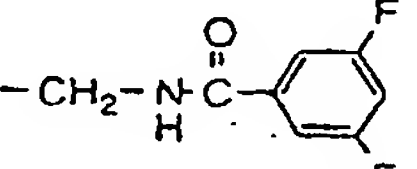
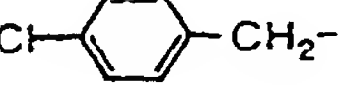
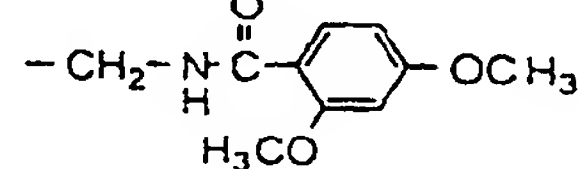
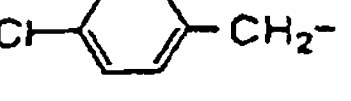
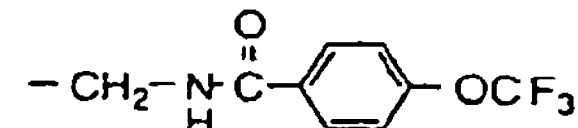
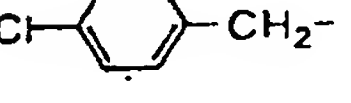
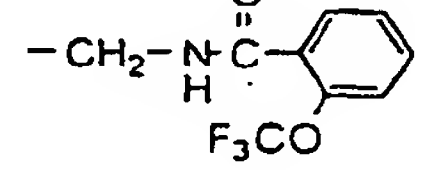
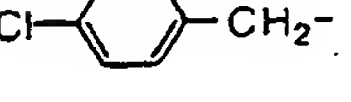
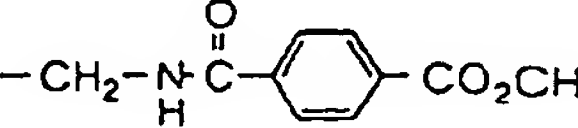
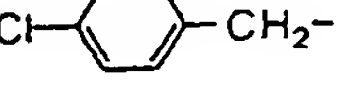
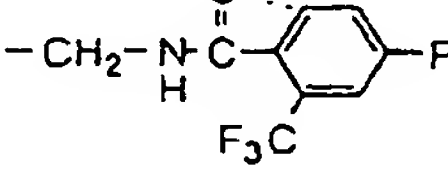
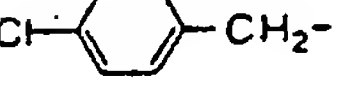
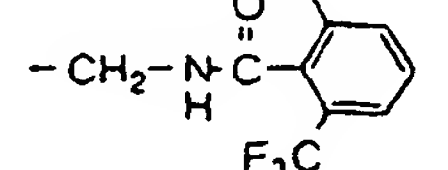
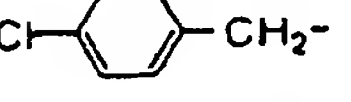
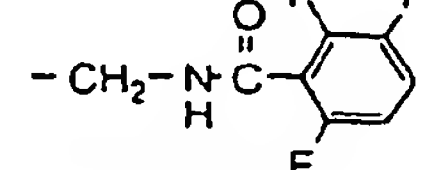
Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (CH_2)_j \text{---}$	k	m	n	chirality	R^3	$-(CH_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} \text{---} (CH_2)_q \text{---} G \text{---} R^6$
67		1	2	0	R	H	
68		1	2	0	R	H	
69		1	2	0	R	H	
70		1	2	0	R	H	
71		1	2	0	R	H	
72		1	2	0	R	H	
73		1	2	0	R	H	
74		1	2	0	R	H	
75		1	2	0	R	H	
76		1	2	0	R	H	
77		1	2	0	R	H	

Table 1.8


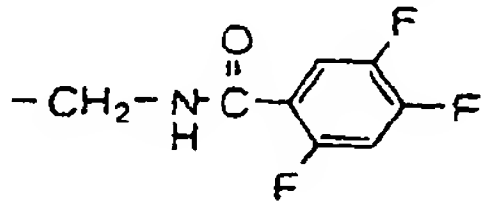
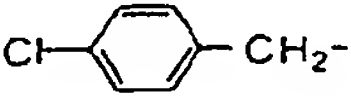
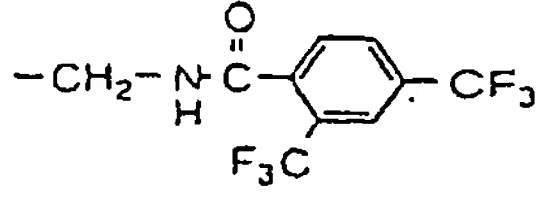
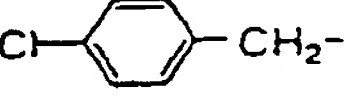
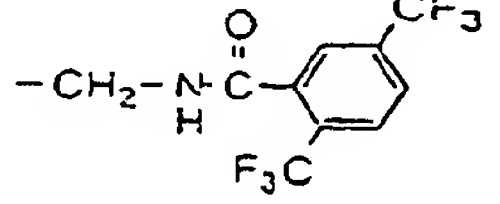
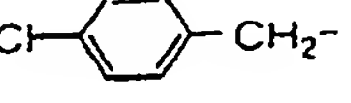
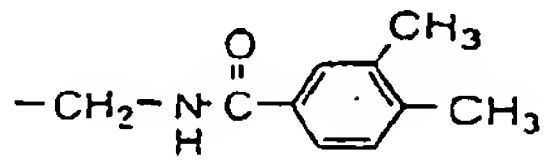
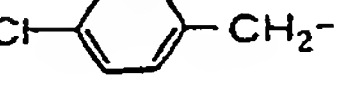
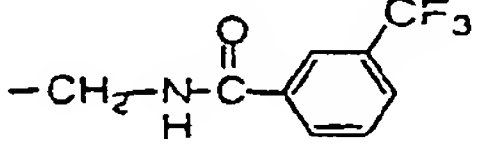

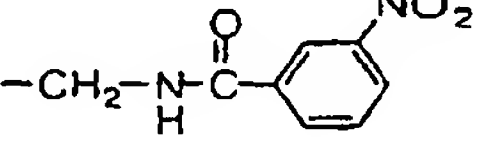
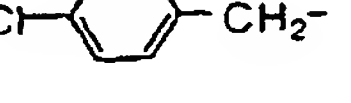
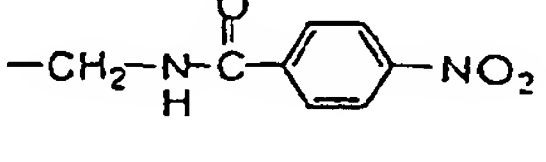
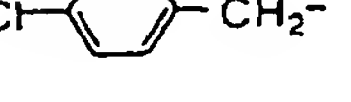
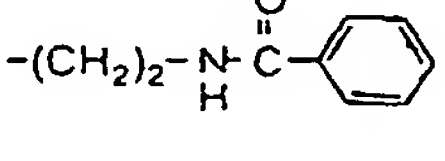
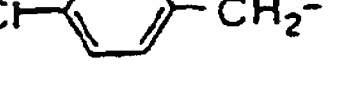
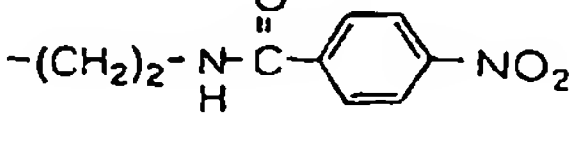
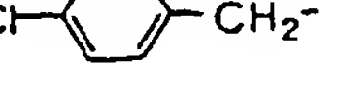
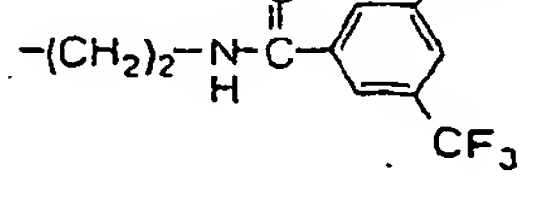
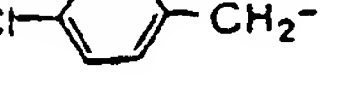
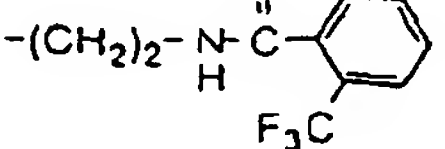
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_k- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p-\overset{\overset{R^4}{ }}{\underset{\underset{R^5}{ }}{C}}-(CH_2)_q-G-R^6$
78		1	2	0	R	H	
79		1	2	0	R	H	
80		1	2	0	R	H	
81		1	2	0	R	H	
82		1	2	0	-	$-CH_3$	
83		1	2	0	R	H	
84		1	2	0	R	H	
85		1	2	0	-	H	
86		1	2	0	-	H	
87		1	2	0	S	H	
88		1	2	0	S	H	

Table 1.9

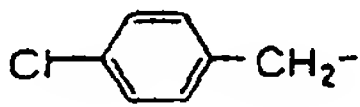
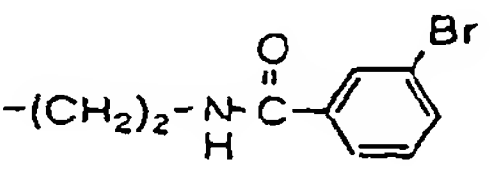

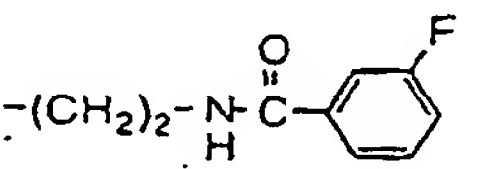
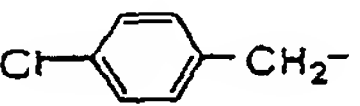
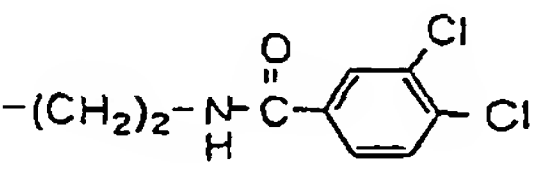
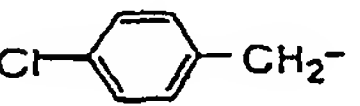
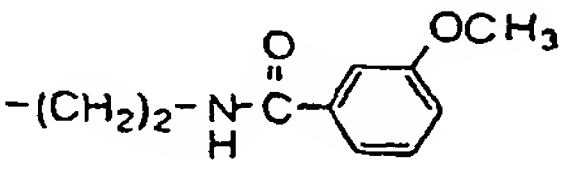
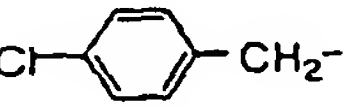
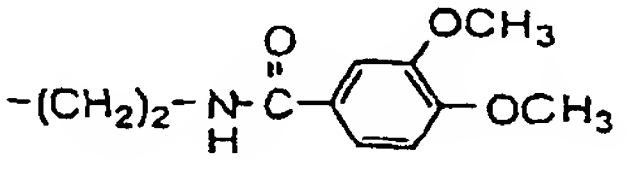
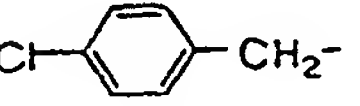
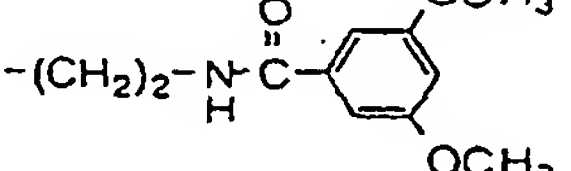
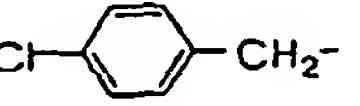
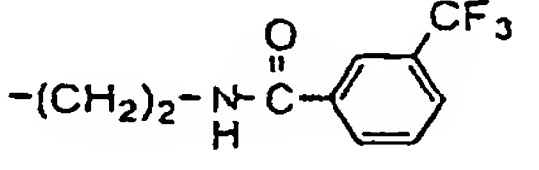
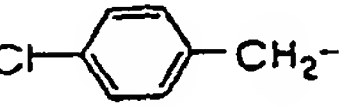
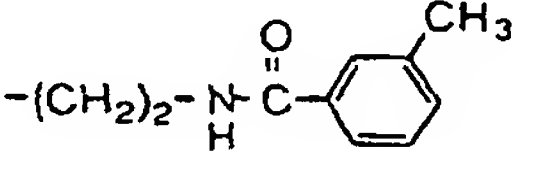
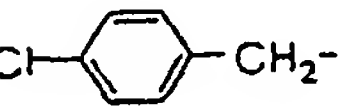
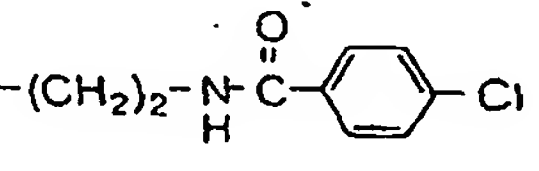
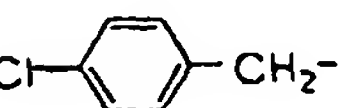
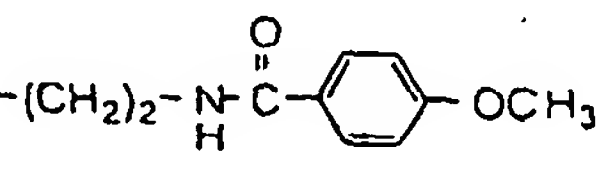
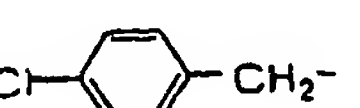
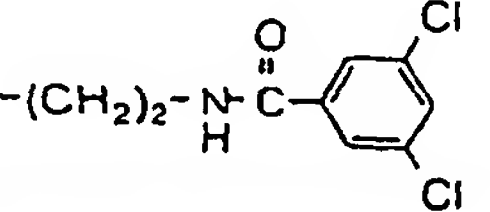
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
89		1	2	0	S	H	
90		1	2	0	S	H	
91		1	2	0	S	H	
92		1	2	0	S	H	
93		1	2	0	S	H	
94		1	2	0	S	H	
95		1	2	0	S	H	
96		1	2	0	S	H	
97		1	2	0	S	H	
98		1	2	0	S	H	
99		1	2	0	S	H	

Table 1.10

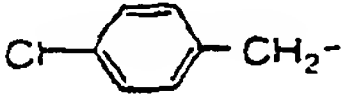
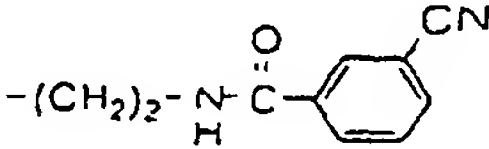
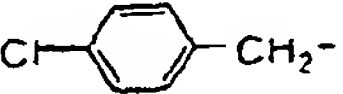
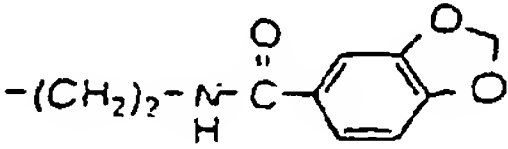
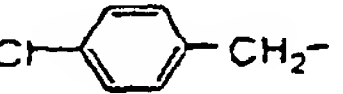
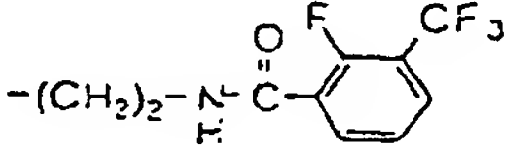
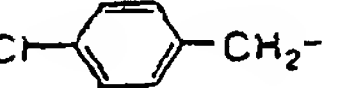
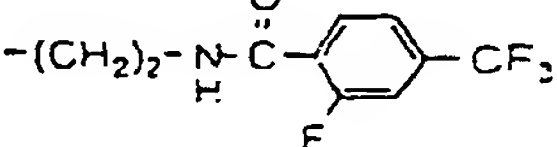
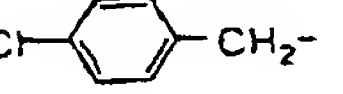
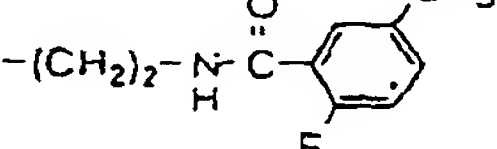
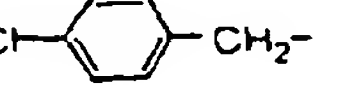
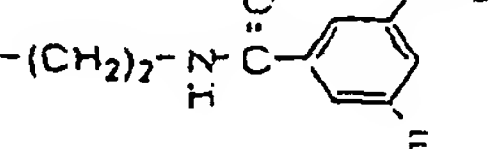
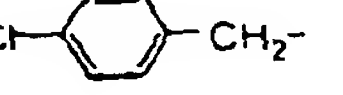
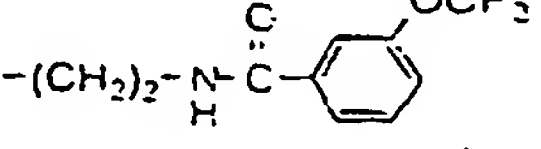
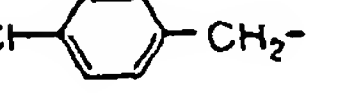
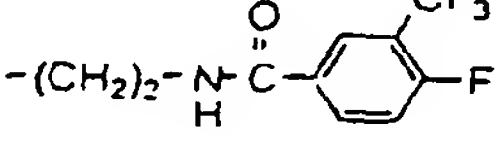
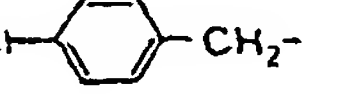
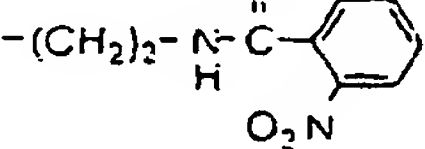
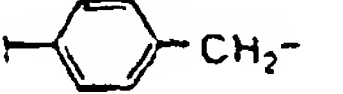
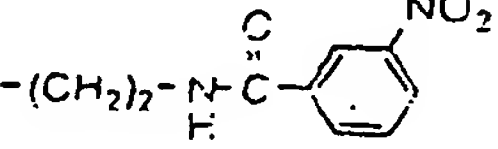
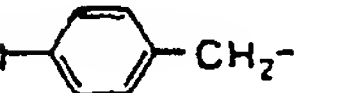
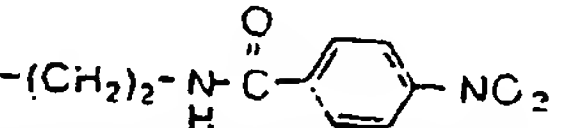
Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (CH_2)_l \text{---}$	k	m	n	chirality	R^3	$-(CH_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} \text{---} (CH_2)_q \text{---} G \text{---} R^i$
100		1	2	0	S	H	
101		1	2	0	S	H	
102		1	2	0	S	H	
103		1	2	0	S	H	
104		1	2	0	S	H	
105		1	2	0	S	H	
106		1	2	0	S	H	
107		1	2	0	S	H	
108		1	2	0	S	H	
109		1	2	0	S	H	
110		1	2	0	S	H	

Table 1.11


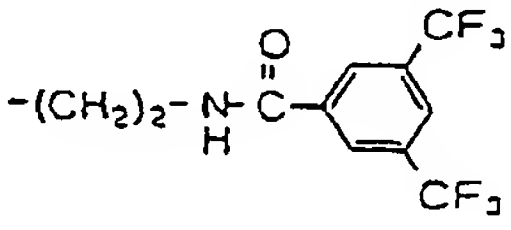
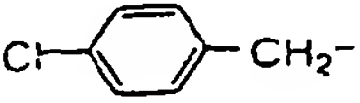
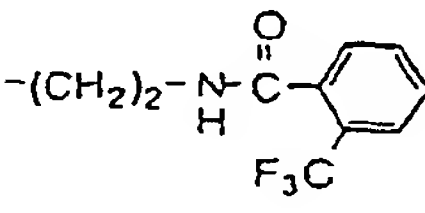
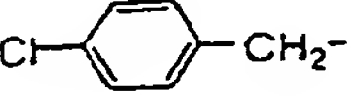
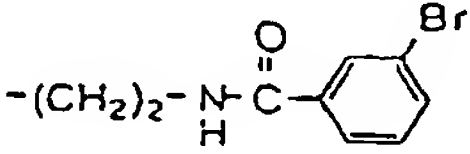
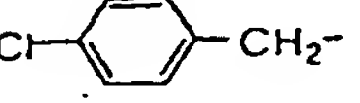
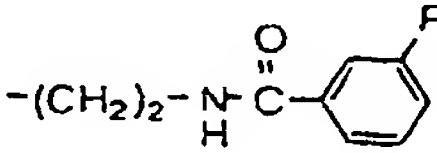
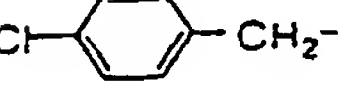
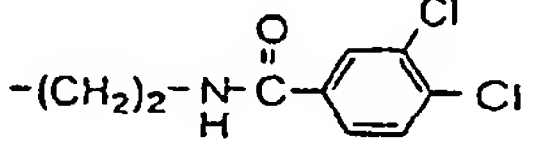
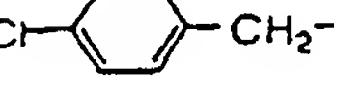
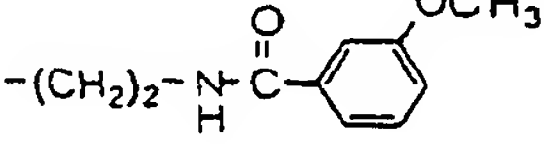
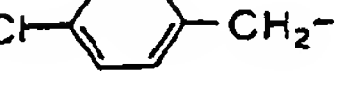
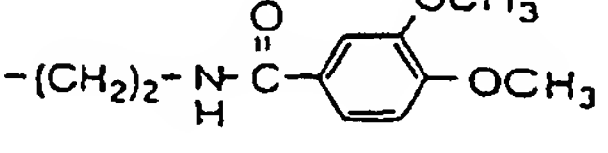
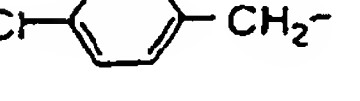
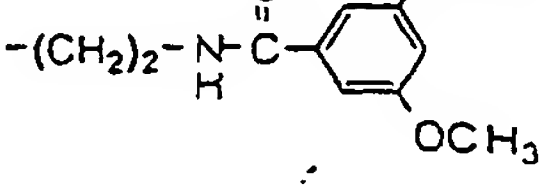
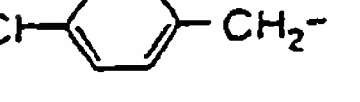
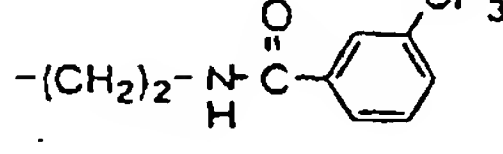
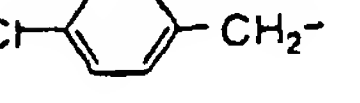
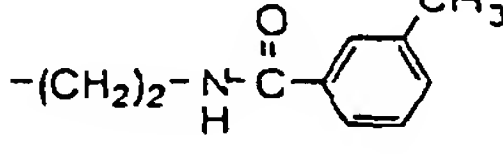
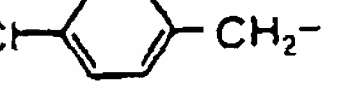
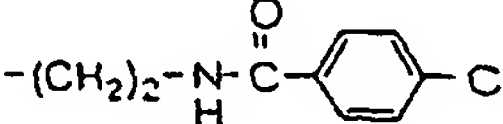
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
111		1	2	0	R	H	
112		1	2	0	R	H	
113		1	2	0	R	H	
114		1	2	0	R	H	
115		1	2	0	R	H	
116		1	2	0	R	H	
117		1	2	0	R	H	
118		1	2	0	R	H	
119		1	2	0	R	H	
120		1	2	0	R	H	
121		1	2	0	R	H	

Table 1.1 2

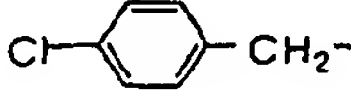
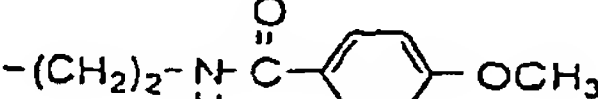
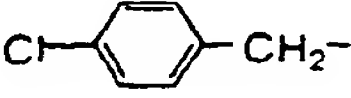
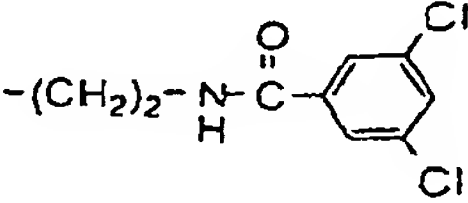
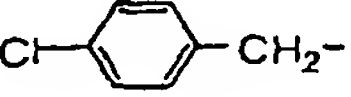
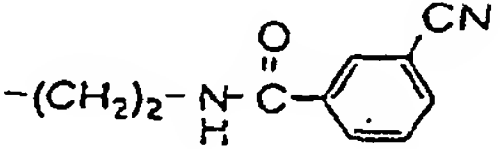
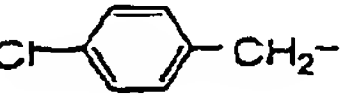
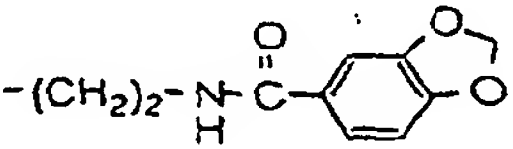
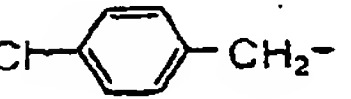
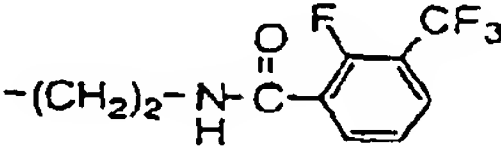
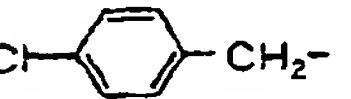
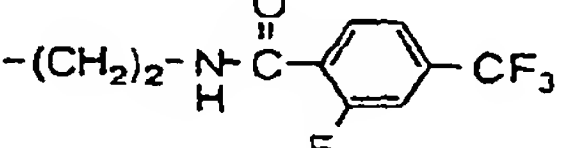
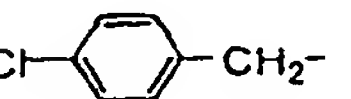
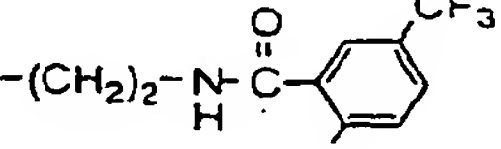
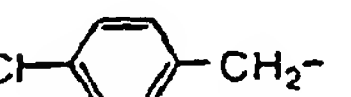
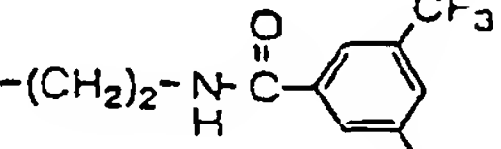
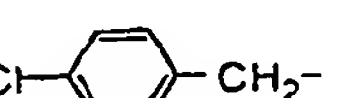
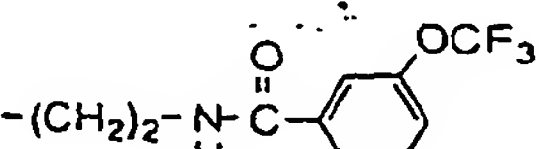
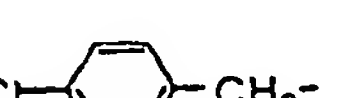
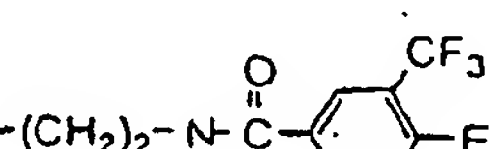

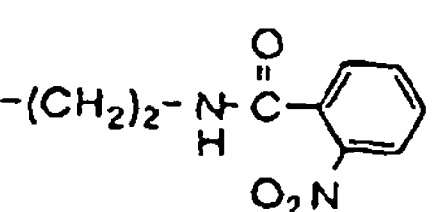
Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ R^2 \end{matrix} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
122		1	2	0	R	H	
123		1	2	0	R	H	
124		1	2	0	R	H	
125		1	2	0	R	H	
126		1	2	0	R	H	
127		1	2	0	R	H	
128		1	2	0	R	H	
129		1	2	0	R	H	
130		1	2	0	R	H	
131		1	2	0	R	H	
132		1	2	0	R	H	

Table 1.13

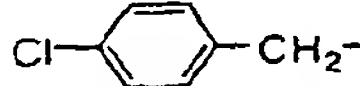
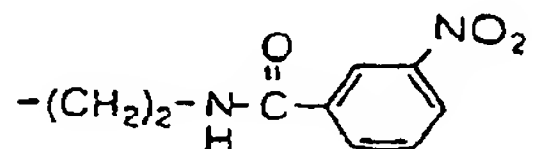
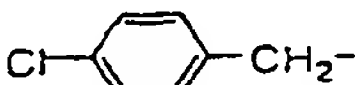
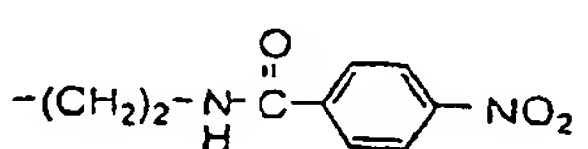

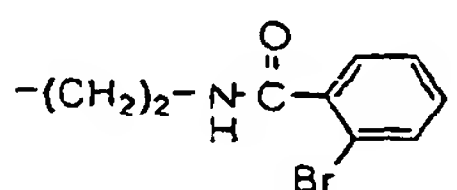

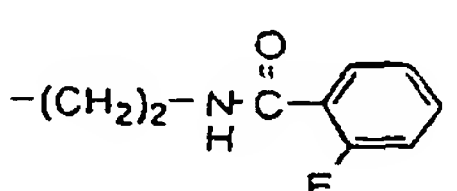

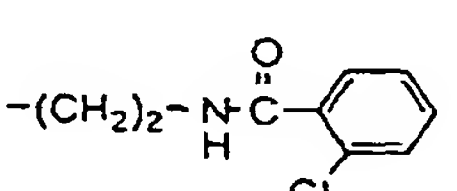

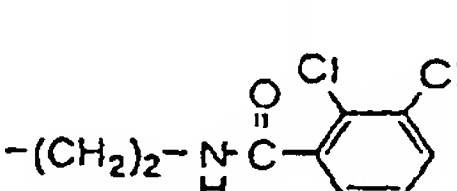

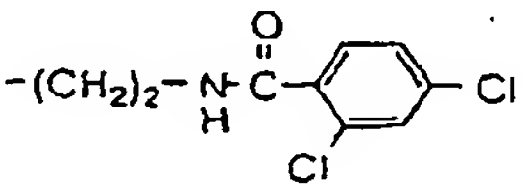

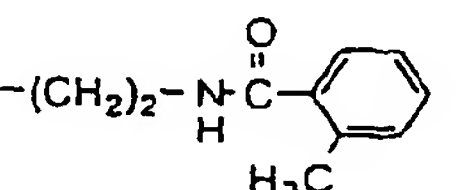

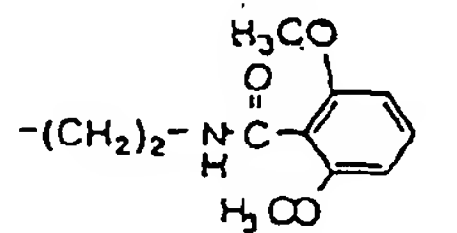

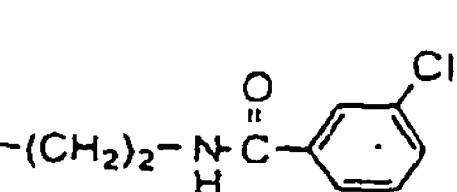

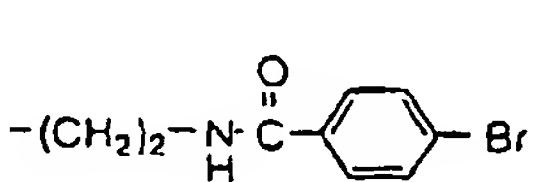
Compd. No.	$\begin{array}{c} R^1 \\ \\ R^2 \end{array} (CH_2)_l -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
133		1	2	0	R	H	
134		1	2	0	R	H	
135		1	2	0	R	H	
136		1	2	0	R	H	
137		1	2	0	R	H	
138		1	2	0	R	H	
139		1	2	0	R	H	
140		1	2	0	R	H	
141		1	2	0	R	H	
142		1	2	0	R	H	
143		1	2	0	R	H	

Table 1.14

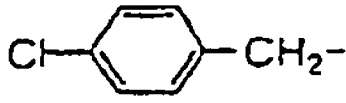
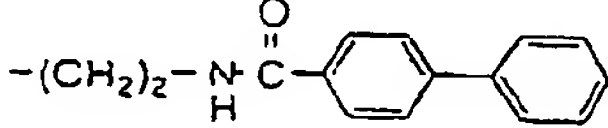
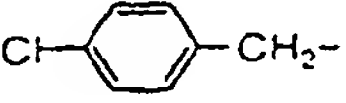
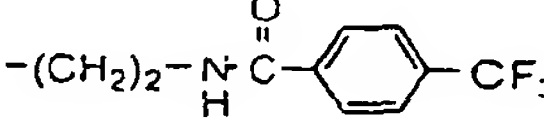
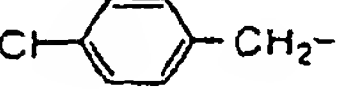
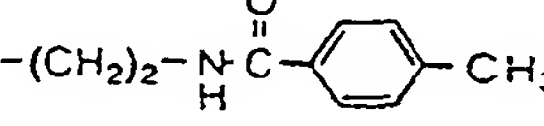
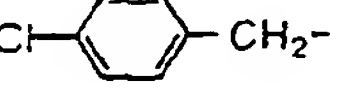
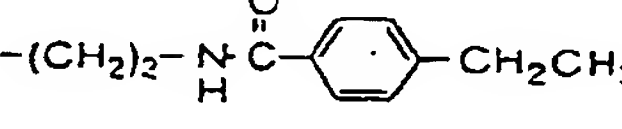
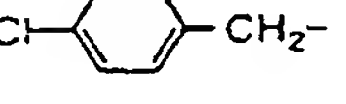
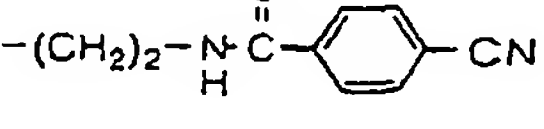
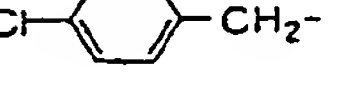
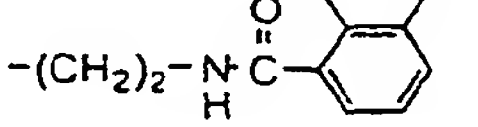
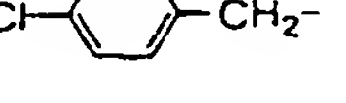
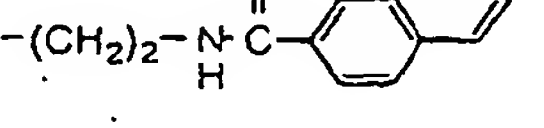
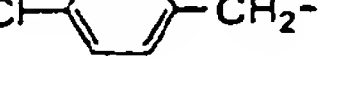
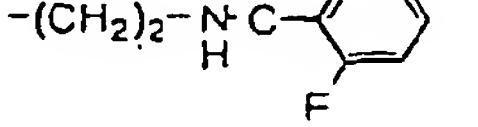
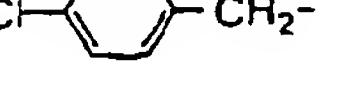
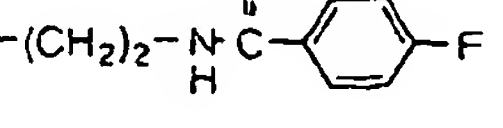
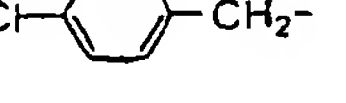
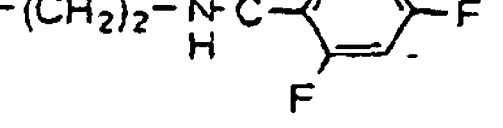
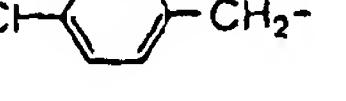
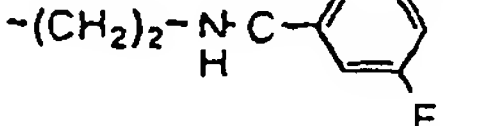
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
144		1	2	0	R	H	
145		1	2	0	R	H	
146		1	2	0	R	H	
147		1	2	0	R	H	
148		1	2	0	R	H	
149		1	2	0	R	H	
150		1	2	0	R	H	
151		1	2	0	R	H	
152		1	2	0	R	H	
153		1	2	0	R	H	
154		1	2	0	R	H	

Table 1.15

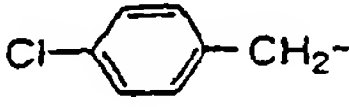
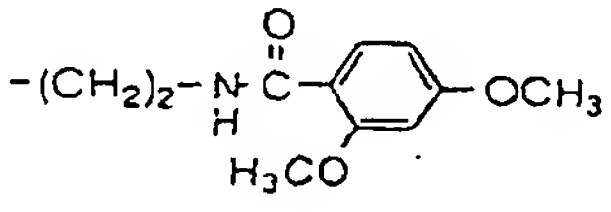
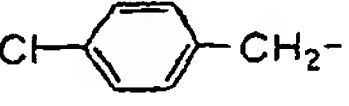
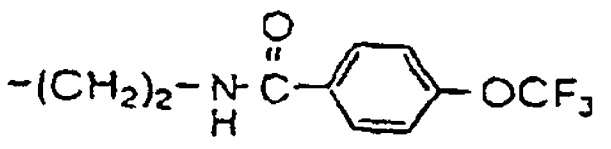
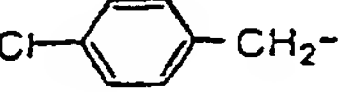
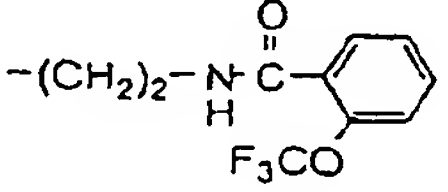
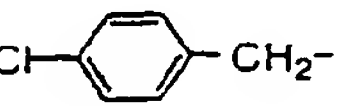
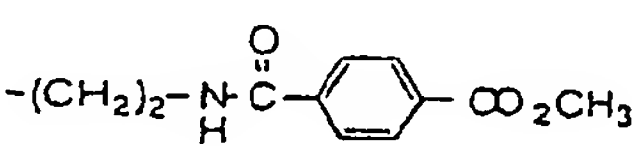
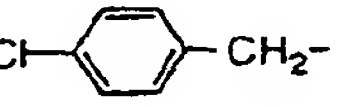
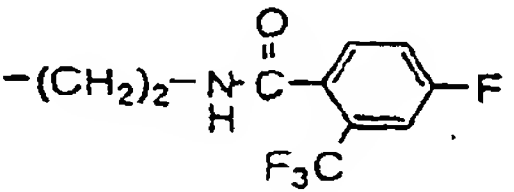
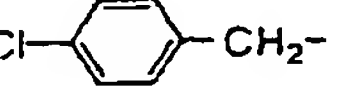
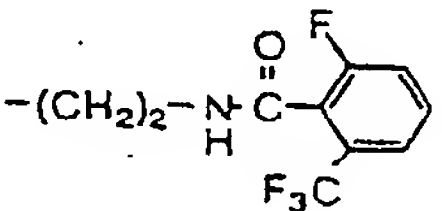
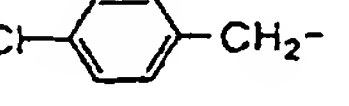
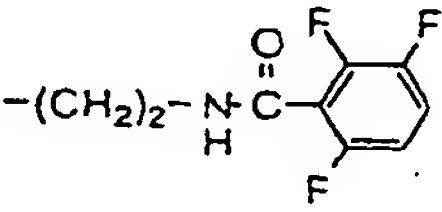
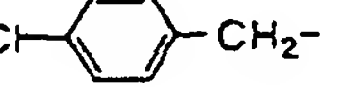
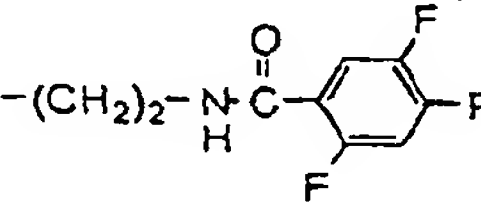
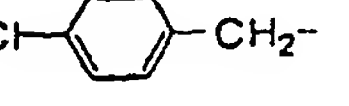
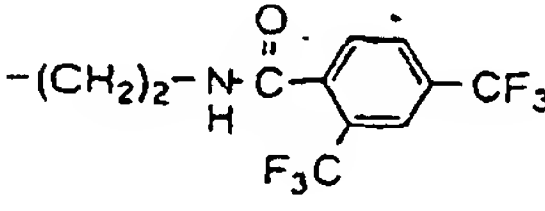
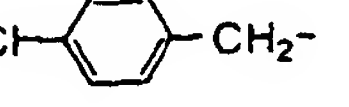
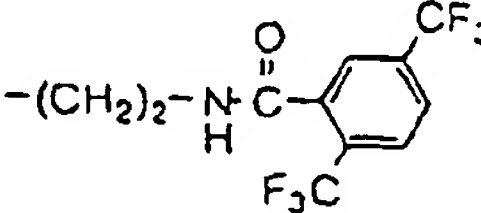
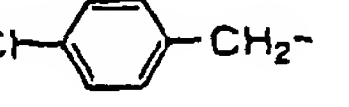
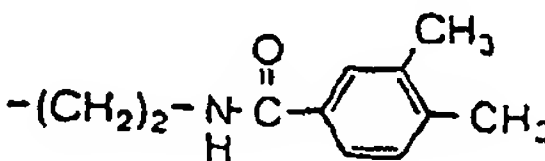
Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (\text{CH}_2)_j \text{---}$	k	m	n	chirality	R^3	$-(\text{CH}_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} \text{---} (\text{CH}_2)_q \text{---} \text{G---} R^6$
155		1	2	0	R	H	
156		1	2	0	R	H	
157		1	2	0	R	H	
158		1	2	0	R	H	
159		1	2	0	R	H	
160		1	2	0	R	H	
161		1	2	0	R	H	
162		1	2	0	R	H	
163		1	2	0	R	H	
164		1	2	0	R	H	
165		1	2	0	R	H	

Table 1.16

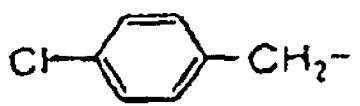
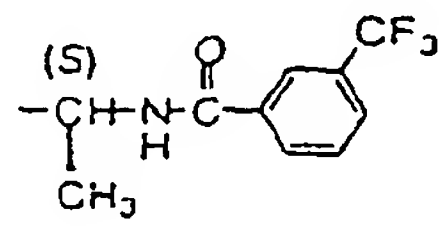
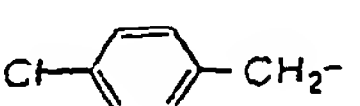
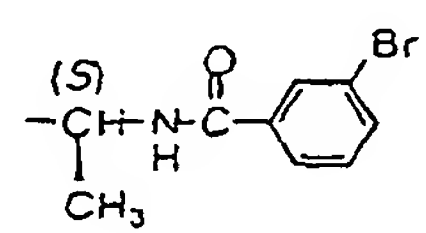

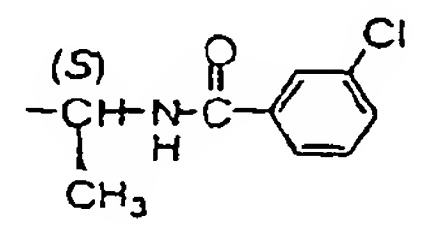
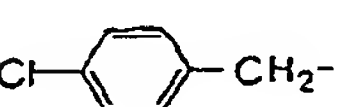
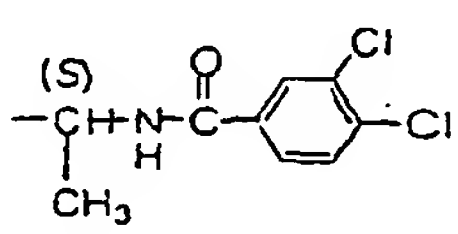
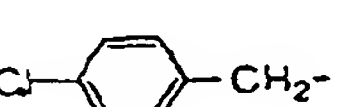
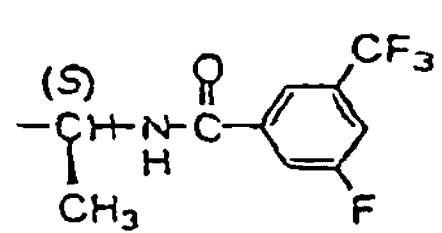
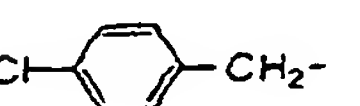
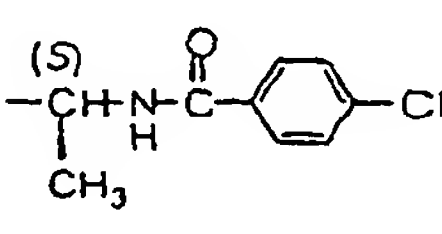
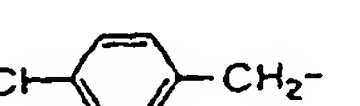
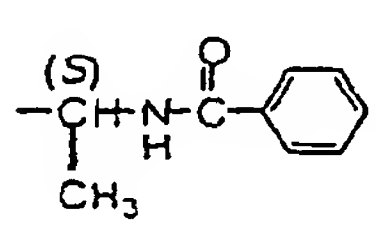
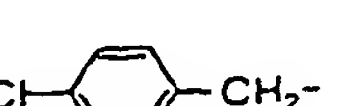
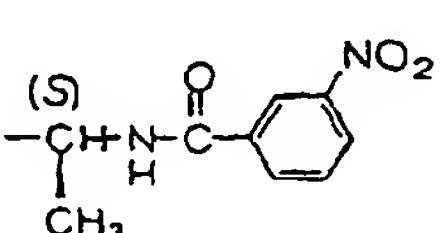

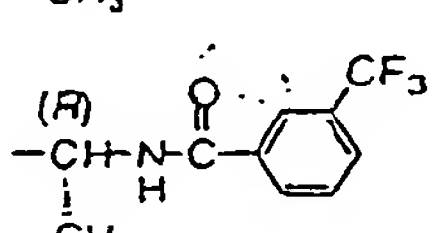
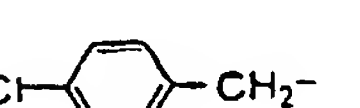
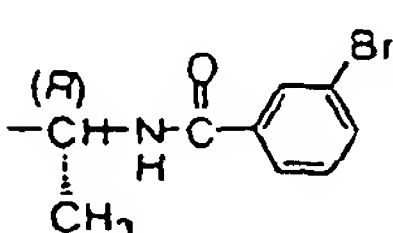

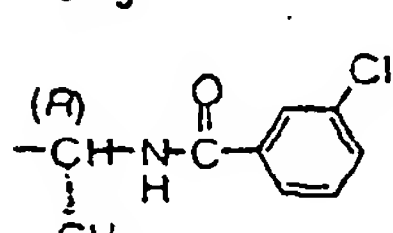
5 10 15 20 25 30 35 40 45 50	Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
	166		1	2	0	R	H	
	167		1	2	0	R	H	
	168		1	2	0	R	H	
	169		1	2	0	R	H	
	170		1	2	0	R	H	
	171		1	2	0	R	H	
	172		1	2	0	R	H	
	173		1	2	0	R	H	
	174		1	2	0	R	H	
	175		1	2	0	R	H	
	176		1	2	0	R	H	

Table 1.17

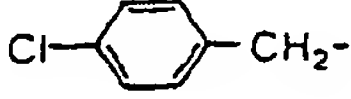
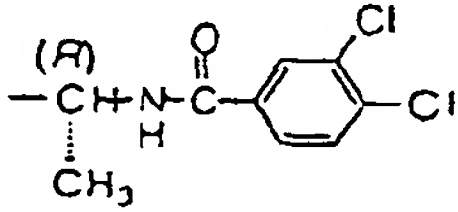
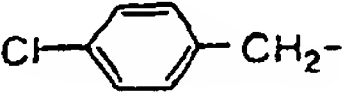
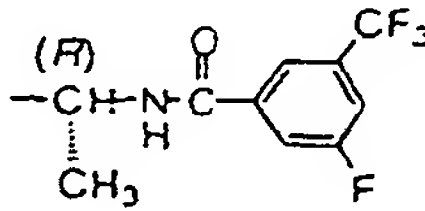
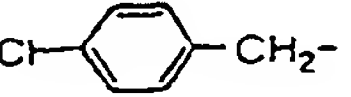
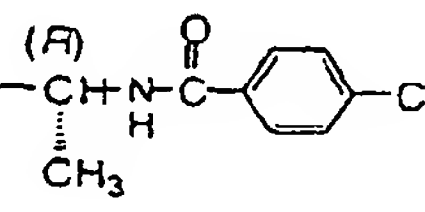

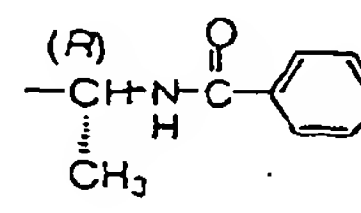
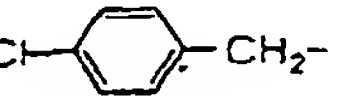
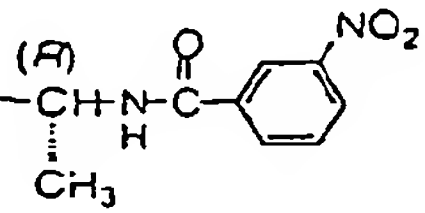
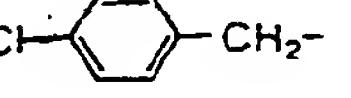
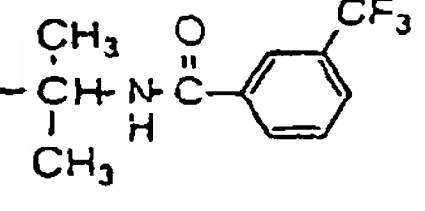
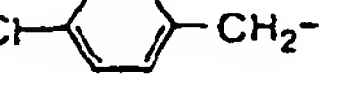
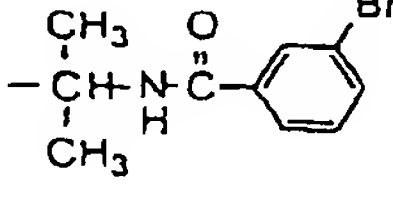

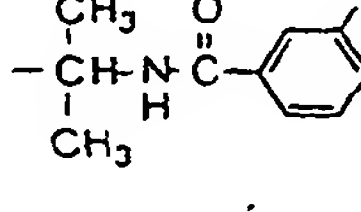
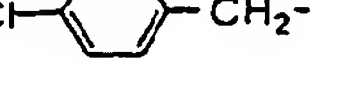
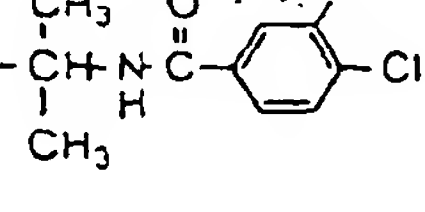
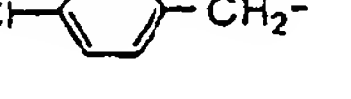
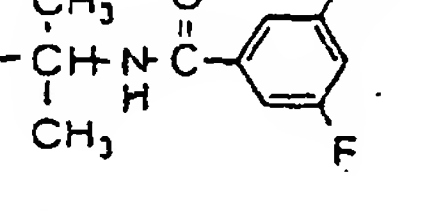
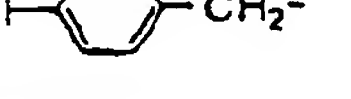
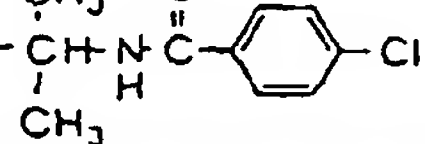
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_l -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
177		1	2	0	R	H	
178		1	2	0	R	H	
179		1	2	0	R	H	
180		1	2	0	R	H	
181		1	2	0	R	H	
182		1	2	0	R	H	
183		1	2	0	R	H	
184		1	2	0	R	H	
185		1	2	0	R	H	
186		1	2	0	R	H	
187		1	2	0	R	H	

Table 1.18

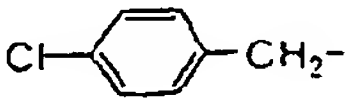
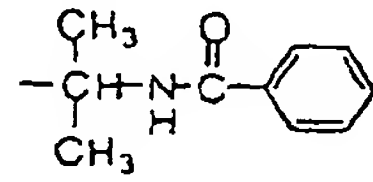
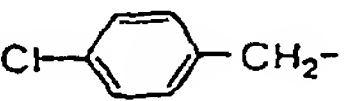
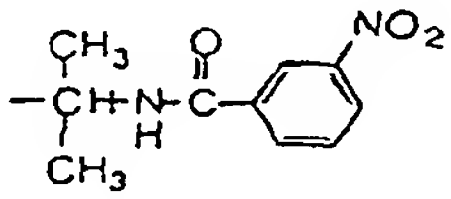
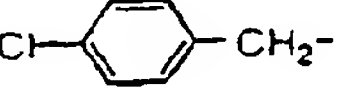
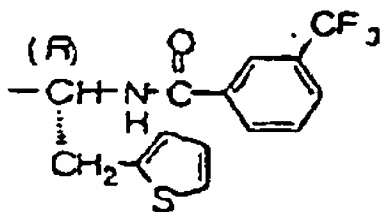

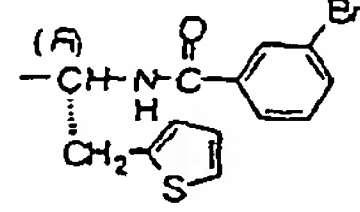
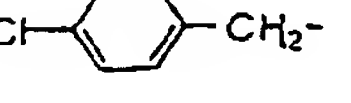
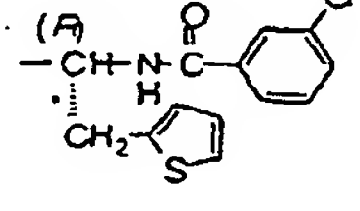
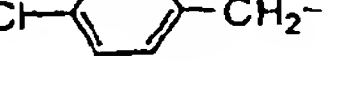
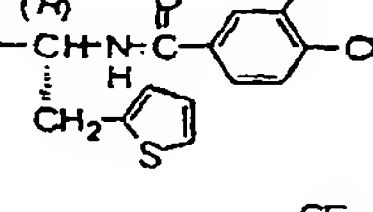

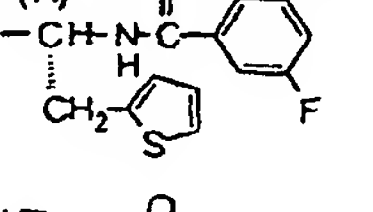

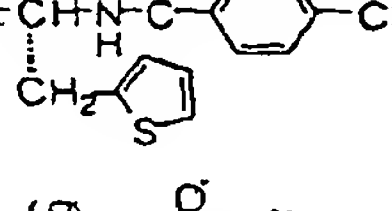

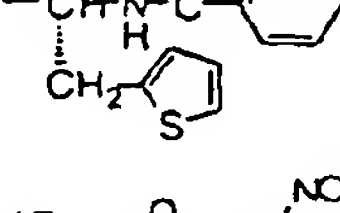

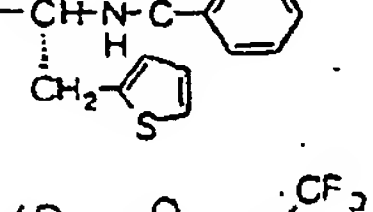

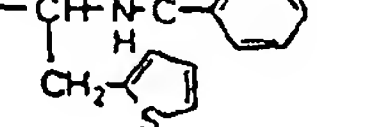
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_k- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q G-R^6$
188		1	2	0	R	H	
189		1	2	0	R	H	
190		1	2	0	R	H	
191		1	2	0	R	H	
192		1	2	0	R	H	
193		1	2	0	R	H	
194		1	2	0	R	H	
195		1	2	0	R	H	
196		1	2	0	R	H	
197		1	2	0	R	H	
198		1	2	0	R	H	

Table 1.1 9

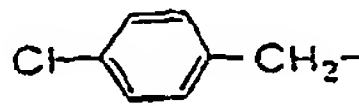
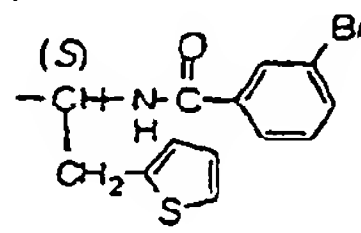
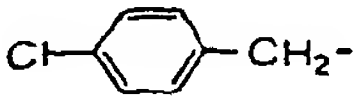
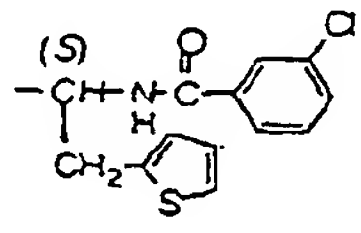
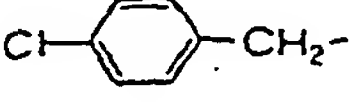
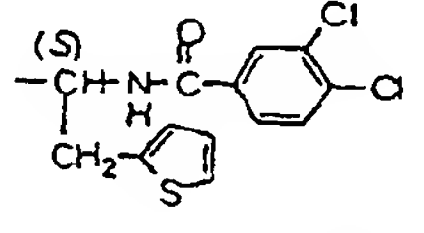
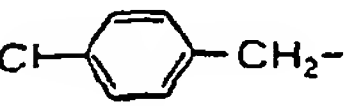
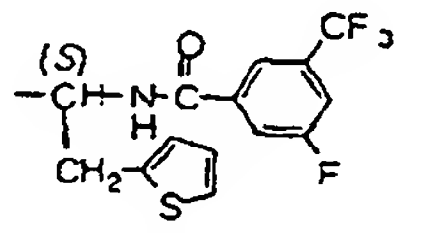
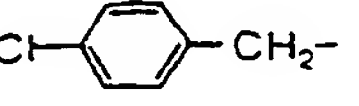
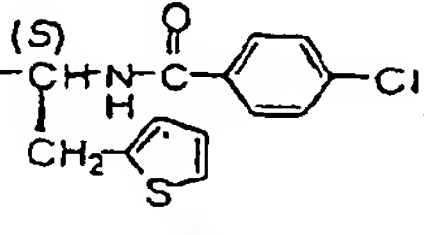
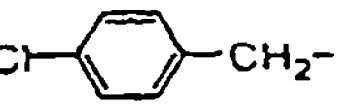
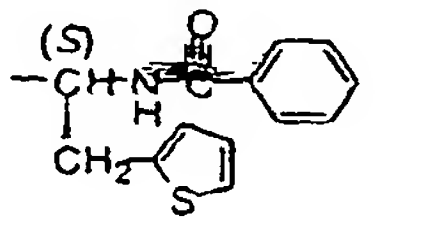
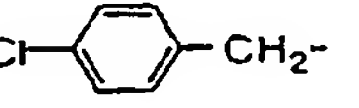
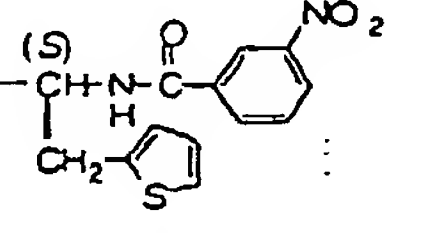
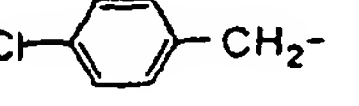
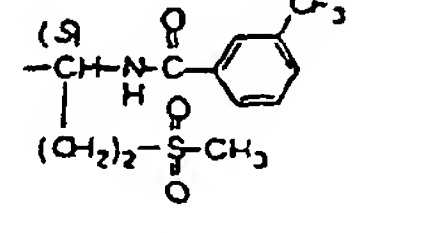
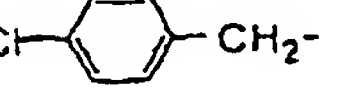
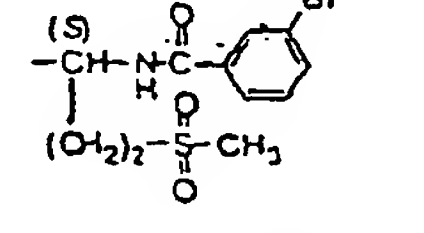
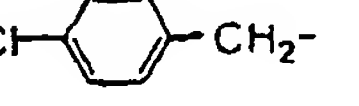
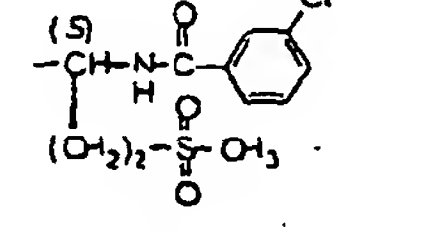
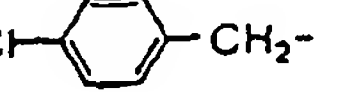
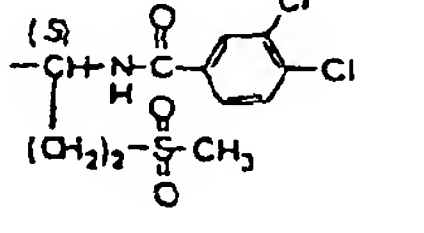
Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (\text{CH}_2)_j \text{---}$	k	m	n	chirality	R^3	$-(\text{CH}_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} \text{---} (\text{CH}_2)_q \text{---} \text{G---} R^6$
199		1	2	0	R	H	
200		1	2	0	R	H	
201		1	2	0	R	H	
202		1	2	0	R	H	
203		1	2	0	R	H	
204		1	2	0	R	H	
205		1	2	0	R	H	
206		1	2	0	R	H	
207		1	2	0	R	H	
208		1	2	0	R	H	
209		1	2	0	R	H	

Table 1.20


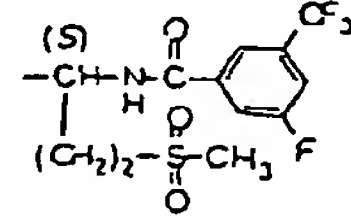
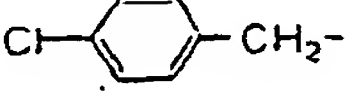
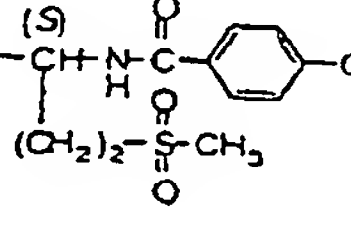
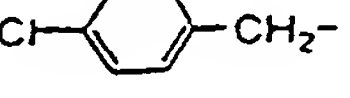
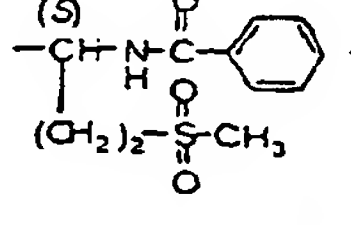
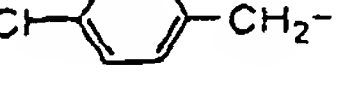
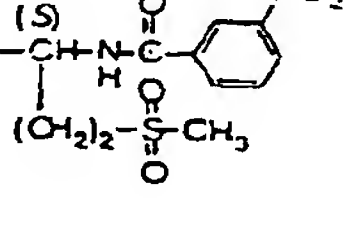
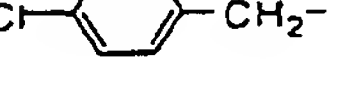
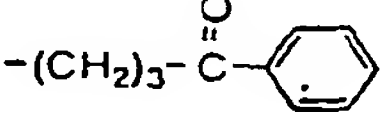

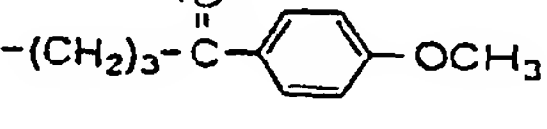

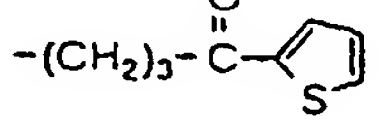

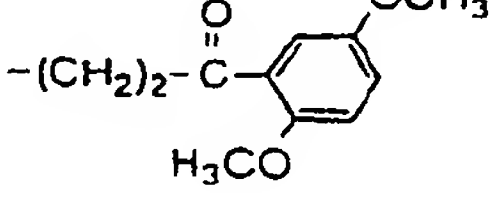

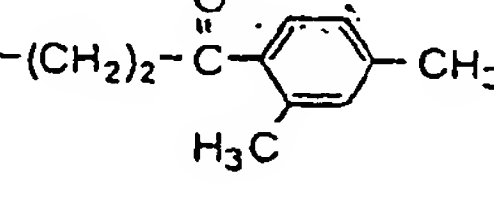

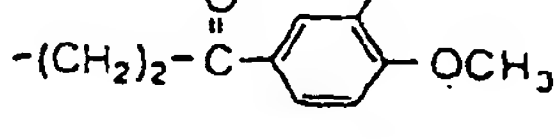

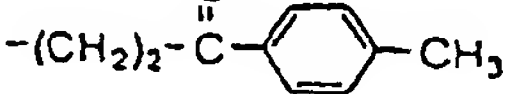
Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ R^2 \end{matrix} (CH_2)_l -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
210		1	2	0	R	H	
211		1	2	0	R	H	
212		1	2	0	R	H	
213		1	2	0	R	H	
214		1	2	0	-	H	
215		1	2	0	-	H	
216		1	2	0	-	H	
217		1	2	0	-	H	
218		1	2	0	-	H	
219		1	2	0	-	H	
220		1	2	0	-	H	

Table 1.21


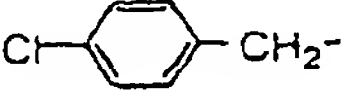
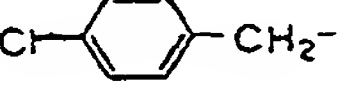

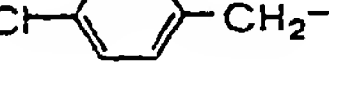
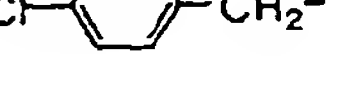




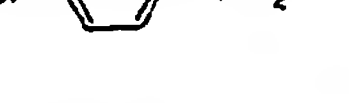
Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (CH_2)_l \text{---}$	k	m	n	chirality	R^3	$-(CH_2)_p \text{---} \begin{matrix} R^4 \\ \\ R^5 \end{matrix} \text{---} (CH_2)_q \text{---} G \text{---} R^6$
221		1	2	0	-	H	$-(CH_2)_2 \text{---} \text{C}(=\text{O}) \text{---} \text{C}_6\text{H}_5$
222		1	2	0	-	H	$-(CH_2)_2 \text{---} \text{C}(=\text{O}) \text{---} \text{C}_6\text{H}_4 \text{---} \text{Cl}$
223		1	2	0	-	H	$-(CH_2)_2 \text{---} \text{C}(=\text{O}) \text{---} \text{C}_6\text{H}_4 \text{---} \text{O}(\text{CH}_2)_3 \text{CH}_3$
224		1	2	0	-	H	$-\text{CH}_2 \text{---} \text{S}(=\text{O})_2 \text{---} \text{C}_6\text{H}_4 \text{---} \text{CH}_3$
225		1	2	0	-	H	$-(CH_2)_3 \text{---} \text{C}(=\text{O}) \text{---} \text{NH} \text{---} \text{C}_6\text{H}_5$
226		1	2	0	-	H	$-(CH_2)_3 \text{---} \text{C}(=\text{O}) \text{---} \text{NH} \text{---} \text{C}_6\text{H}_4 \text{---} \text{OCH}_3$
227		1	2	0	-	H	$-(CH_2)_3 \text{---} \text{C}(=\text{O}) \text{---} \text{NH} \text{---} \text{C}_6\text{H}_4 \text{---} \text{Cl}$
228		1	2	0	-	H	$-(CH_2)_3 \text{---} \text{C}(=\text{O}) \text{---} \text{NH} \text{---} \text{C}_6\text{H}_4 \text{---} \text{OCH}_3$
229		1	2	0	-	H	$-\text{CH}_2 \text{---} \text{C}(\text{CH}_3)_2 \text{---} \text{CH}_2 \text{---} \text{C}(=\text{O}) \text{---} \text{NH} \text{---} \text{C}_6\text{H}_4 \text{---} \text{CH}_3$
230		1	2	0	-	H	$-\text{CH}_2 \text{---} \text{C}_5\text{H}_9 \text{---} \text{CH}_2 \text{---} \text{C}(=\text{O}) \text{---} \text{NH} \text{---} \text{C}_6\text{H}_4 \text{---} \text{F}$
231		1	2	0	-	H	$-(CH_2)_3 \text{---} \text{C}(=\text{O}) \text{---} \text{NH} \text{---} \text{C}_6\text{H}_4 \text{---} \text{C}(=\text{O}) \text{---} \text{CH}_3$

Table 1.2.2

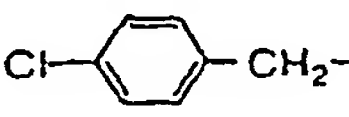
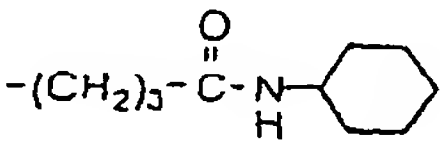
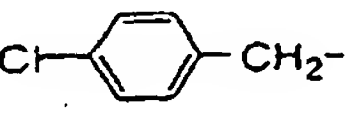
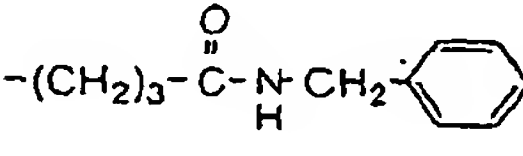
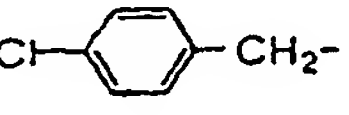
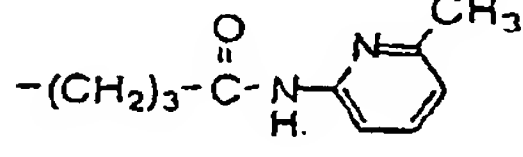
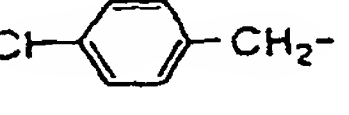
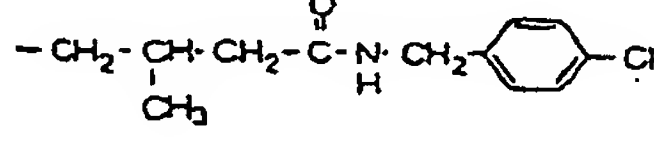
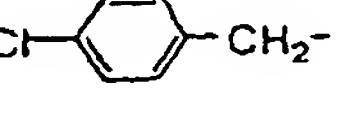
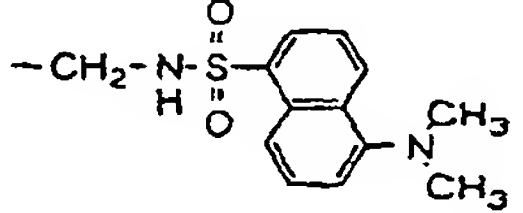
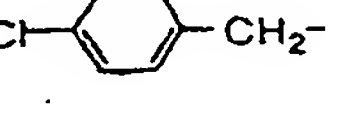
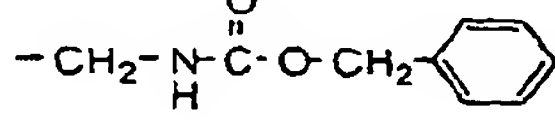
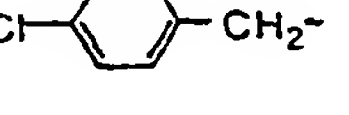
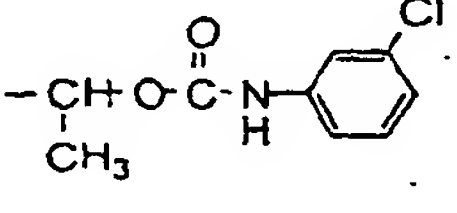
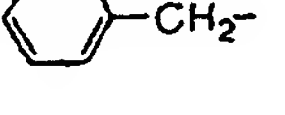
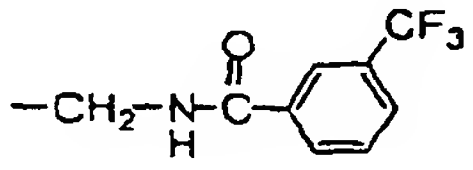
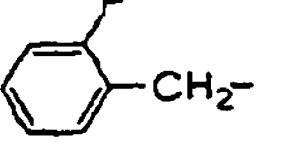
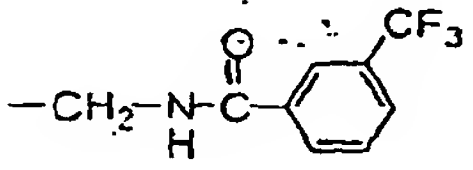
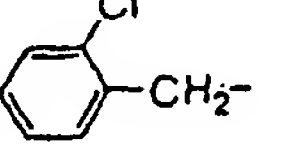
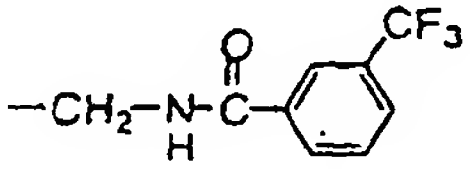
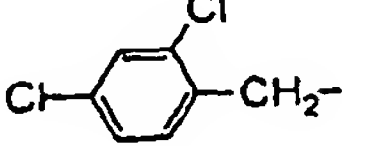
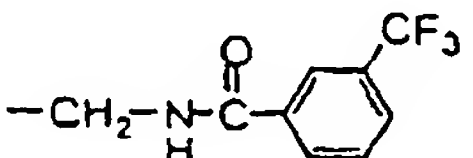
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ (CH_2)_q \\ \\ R^5 \end{array} G-R^6$
232		1	2	0	-	H	
233		1	2	0	-	H	
234		1	2	0	-	H	
235		1	2	0	-	H	
236		1	2	0	-	H	
237		1	2	0	-	H	
238		1	2	0	-	H	
239		1	2	0	S	H	
240		1	2	0	S	H	
241		1	2	0	S	H	
242		1	2	0	S	H	

Table 1.23

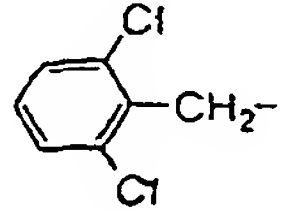
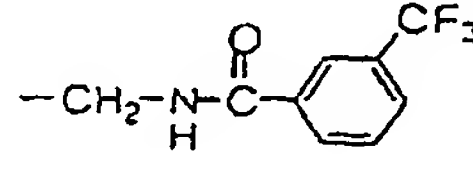
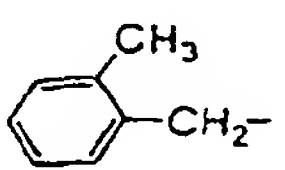
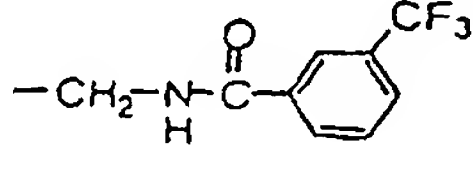
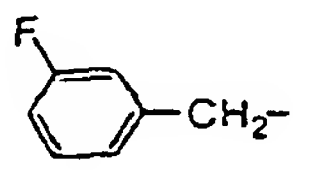
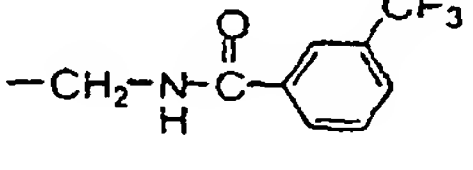
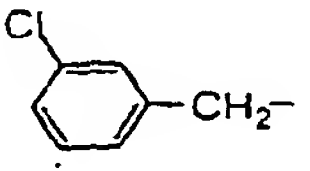
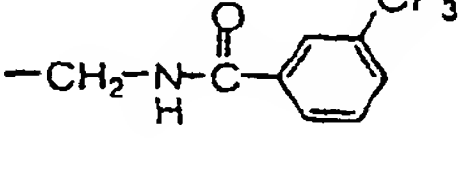
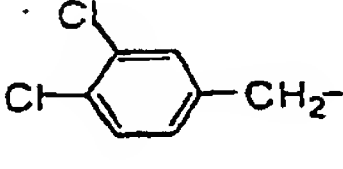
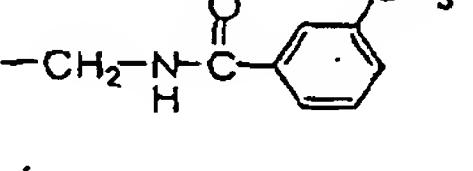
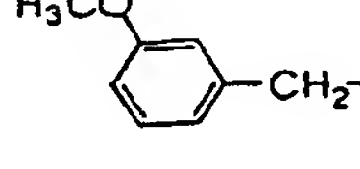
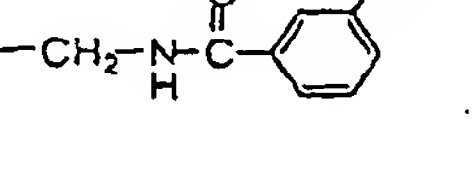
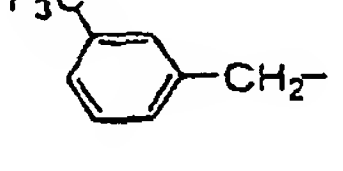
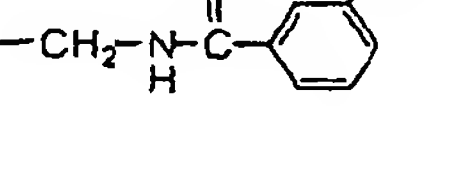
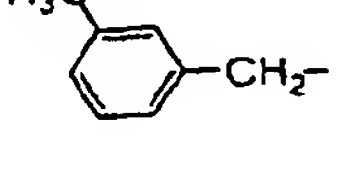
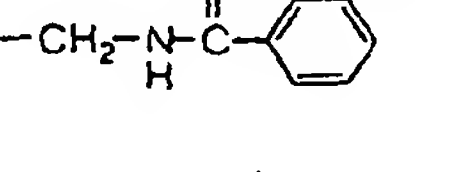
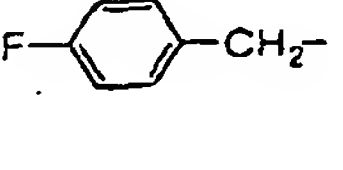
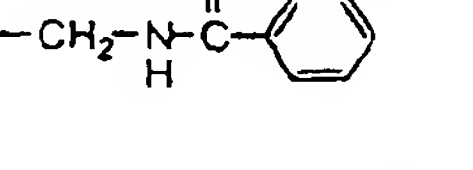
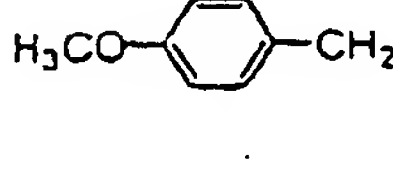
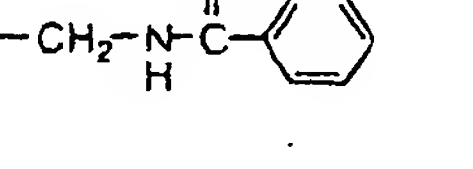
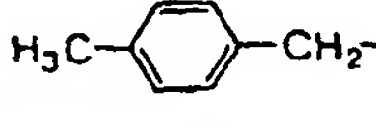
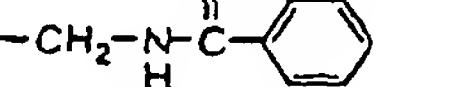
Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ R^2 \end{matrix} (CH_2)_j$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
243		1	2	0	S	H	
244		1	2	0	S	H	
245		1	2	0	S	H	
246		1	2	0	S	H	
247		1	2	0	S	H	
248		1	2	0	S	H	
249		1	2	0	S	H	
250		1	2	0	S	H	
251		1	2	0	S	H	
252		1	2	0	S	H	
253		1	2	0	S	H	

Table 1.2 4

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_i \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ -C- \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
254		1	2	0	S	H	
255		1	2	0	S	H	
256		1	2	0	S	H	
257		1	2	0	S	H	
258		1	2	0	S	H	
259		1	2	0	S	H	
260		1	2	0	S	H	
261		1	2	0	S	H	
262		1	2	0	S	H	
263		1	2	0	S	H	
264		1	2	0	S	H	

Table 1.2 5

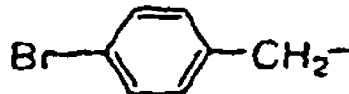
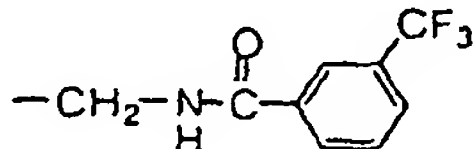
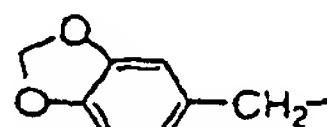
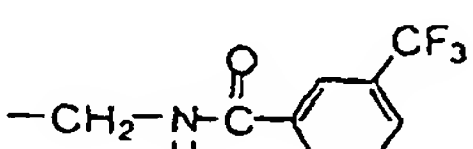
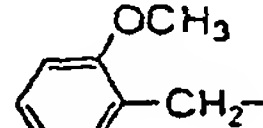
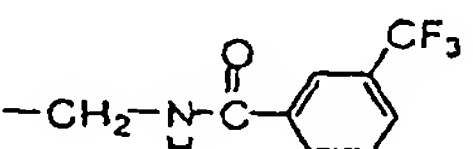
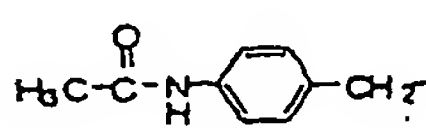
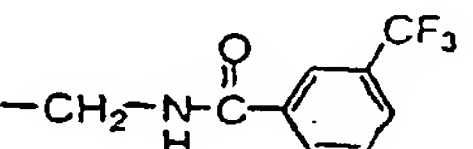
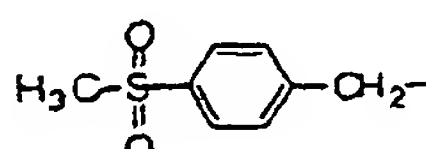
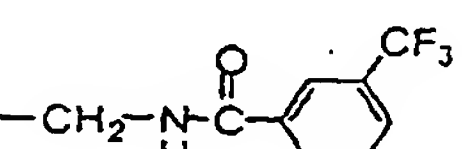
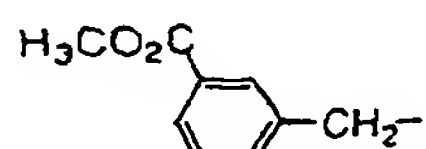
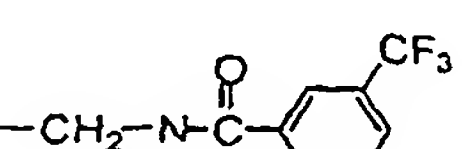
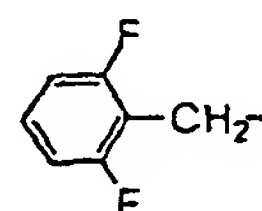
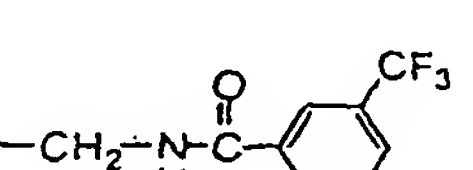
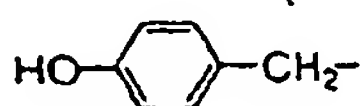
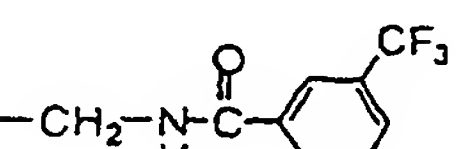
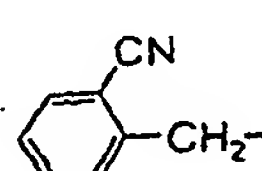
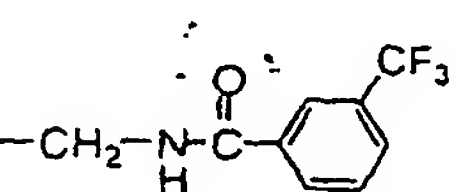
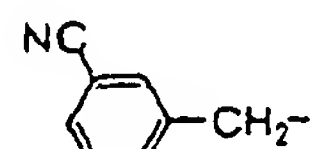
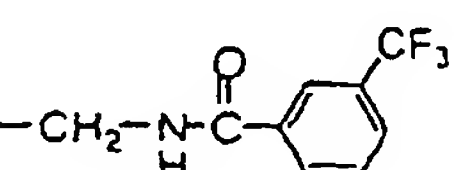
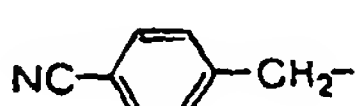
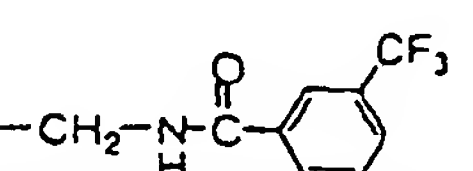
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
265		1	2	0	S	H	
266		1	2	0	S	H	
267		1	2	0	S	H	
268		1	2	0	S	H	
269		1	2	0	S	H	
270		1	2	0	S	H	
271		1	2	0	S	H	
272		1	2	0	S	H	
273		1	2	0	S	H	
274		1	2	0	S	H	
275		1	2	0	S	H	

Table 1.2 6

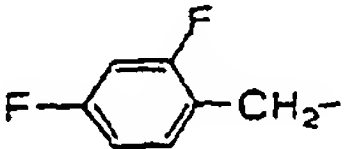
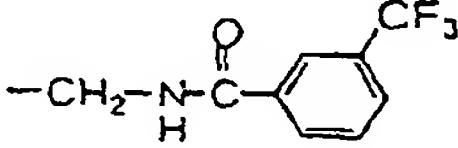
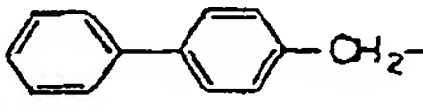
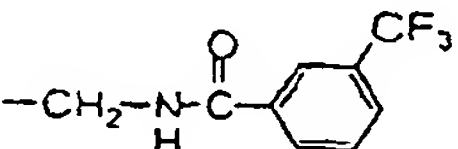
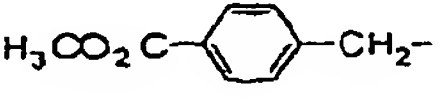
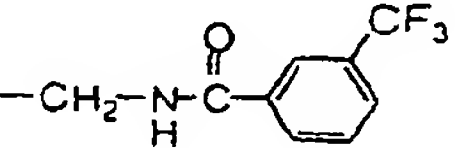

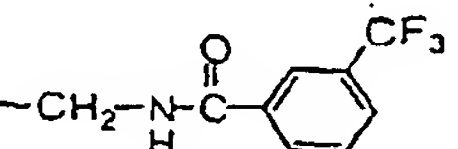
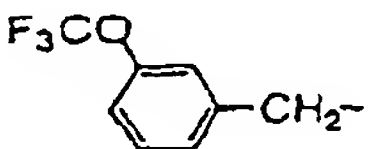
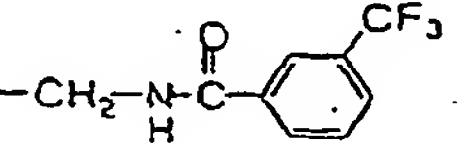

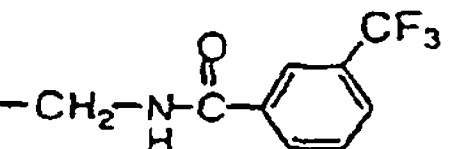
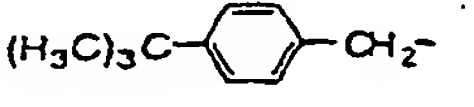
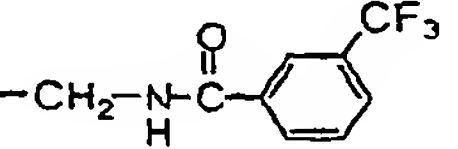
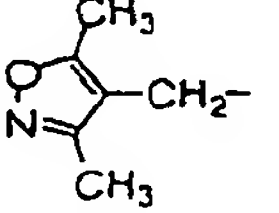
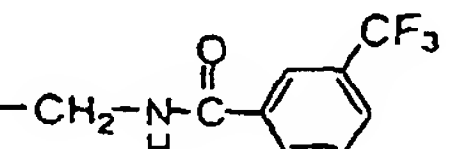
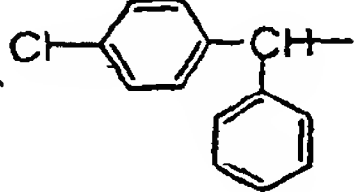
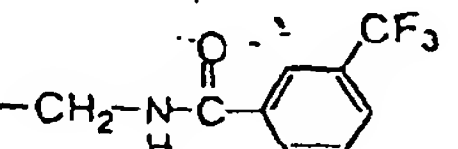
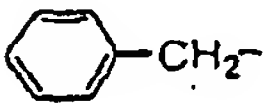
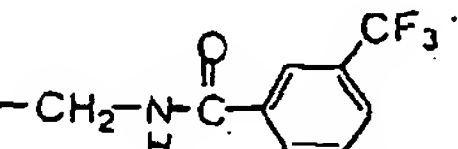
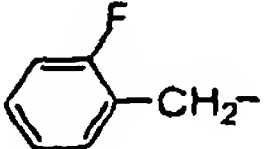
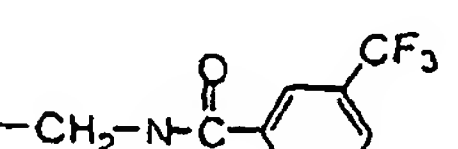
Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (\text{CH}_2)_j \text{---}$	k	m	n	chirality	R^3	$-(\text{CH}_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} \text{---} (\text{CH}_2)_q \text{---} \text{G---} R^6$
276		1	2	0	S	H	
277		1	2	0	S	H	
278		1	2	0	S	H	
279		1	2	0	S	H	
280		1	2	0	S	H	
281		1	2	0	S	H	
282		1	2	0	S	H	
283		1	2	0	S	H	
284		1	2	0	S	H	
285		1	2	0	R	H	
286		1	2	0	R	H	

Table 1.27

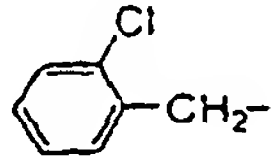
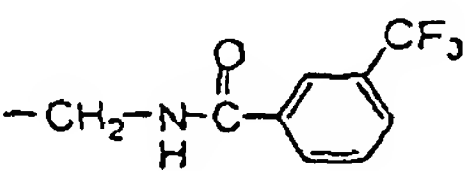
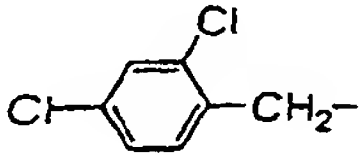
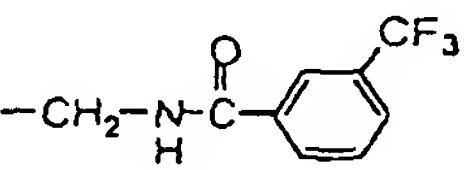
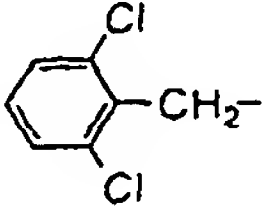
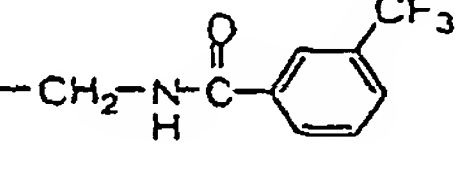
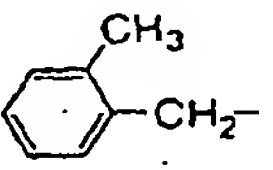
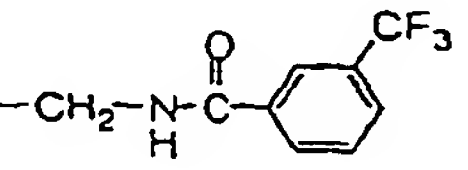
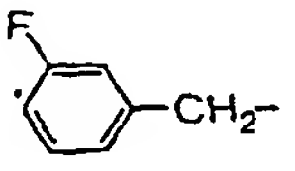
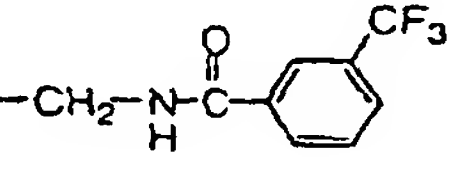
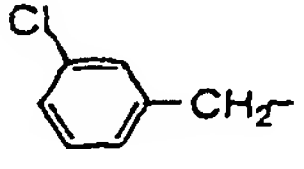
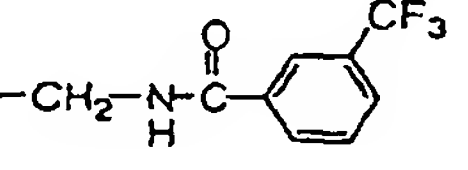
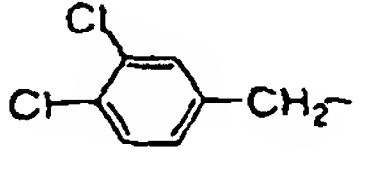
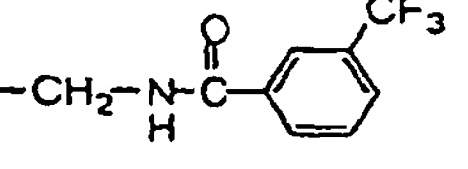
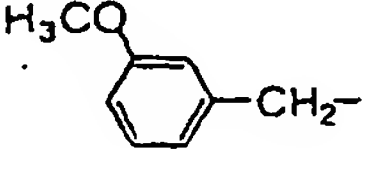
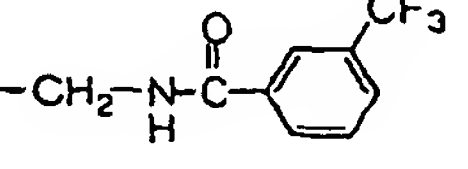
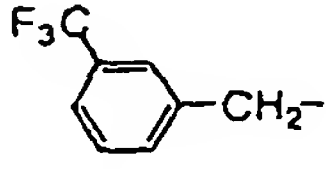
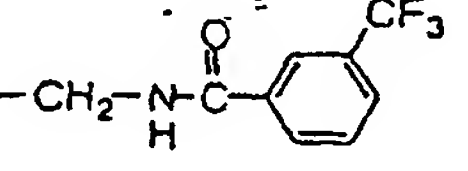
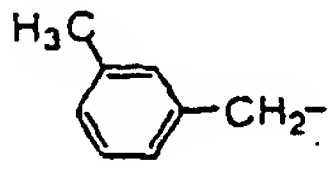
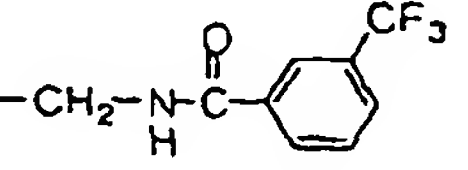
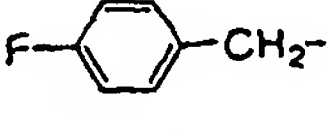
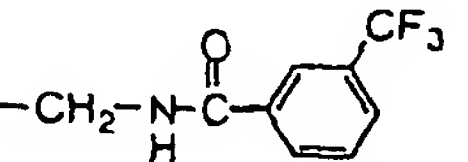
Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ (CH_2)_k \\ \diagdown \\ R^2 \end{matrix}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ (CH_2)_q \\ \\ R^5 \end{matrix} G-R^6$
287		1	2	0	R	H	
288		1	2	0	R	H	
289		1	2	0	R	H	
290		1	2	0	R	H	
291		1	2	0	R	H	
292		1	2	0	R	H	
293		1	2	0	R	H	
294		1	2	0	R	H	
295		1	2	0	R	H	
296		1	2	0	R	H	
297		1	2	0	R	H	

Table 1.2 8

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_i$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
298		1	2	0	R	H	
299		1	2	0	R	H	
300		1	2	0	R	H	
301		1	2	0	R	H	
302		1	2	0	R	H	
303		1	2	0	R	H	
304		1	2	0	R	H	
305		1	2	0	R	H	
306		1	2	0	R	H	
307		1	2	0	R	H	
308		1	2	0	R	H	

Table 1.2 9

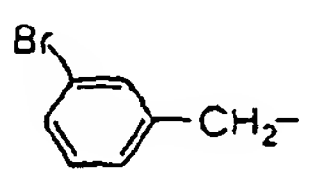
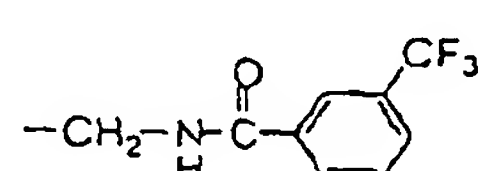
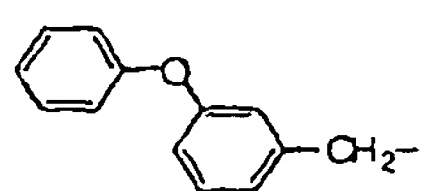
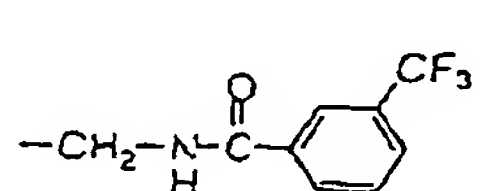
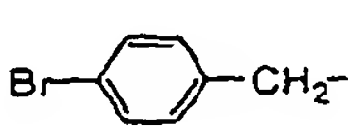
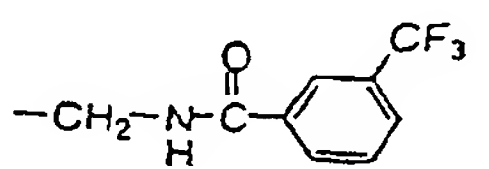
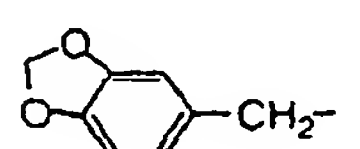
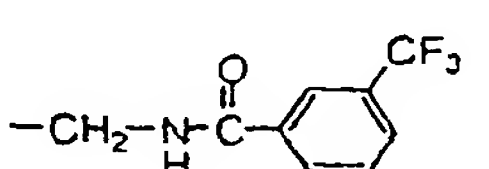
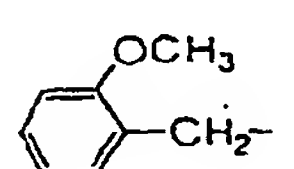
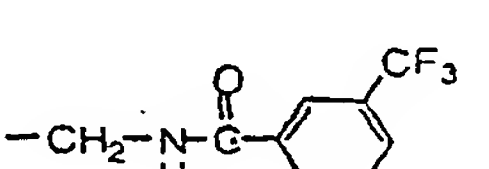

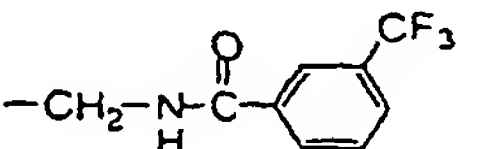
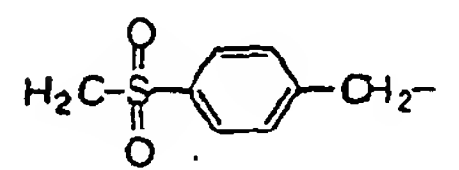
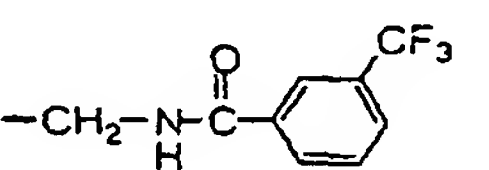
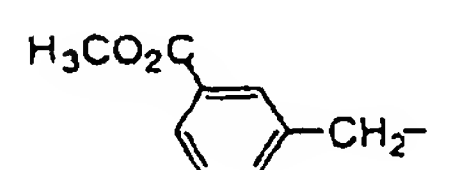
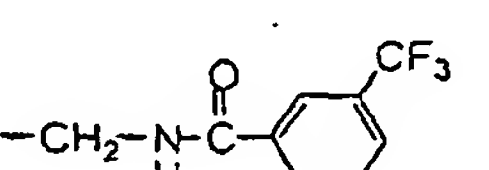
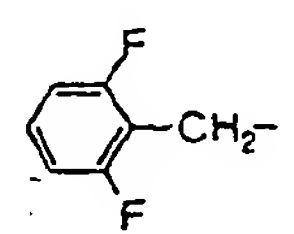
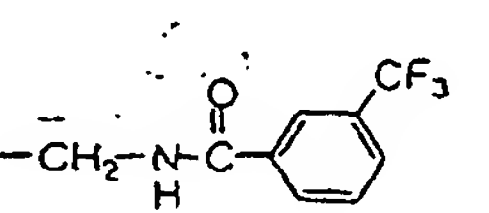
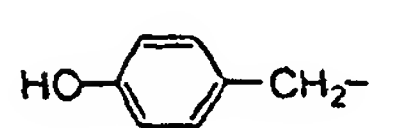
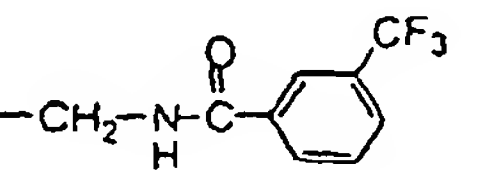
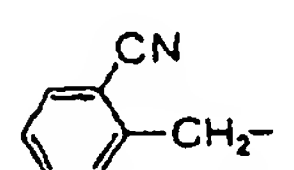
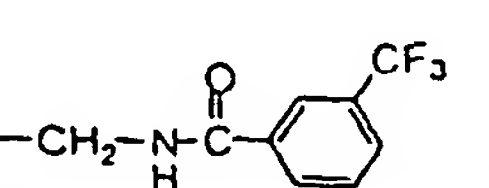
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
309		1	2	0	R	H	
310		1	2	0	R	H	
311		1	2	0	R	H	
312		1	2	0	R	H	
313		1	2	0	R	H	
314		1	2	0	R	H	
315		1	2	0	R	H	
316		1	2	0	R	H	
317		1	2	0	R	H	
318		1	2	0	R	H	
319		1	2	0	R	H	

Table 1.30

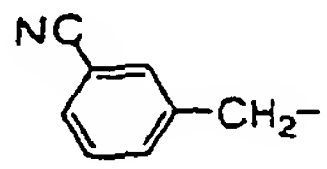
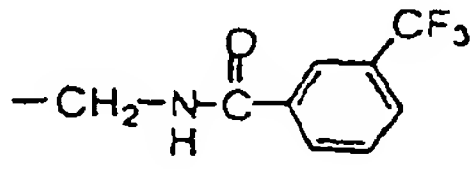
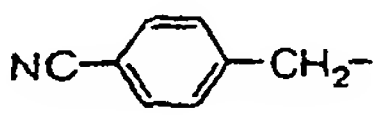
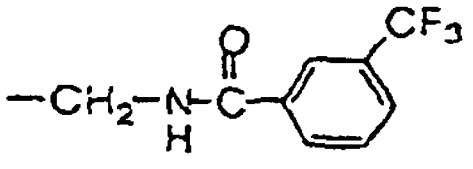
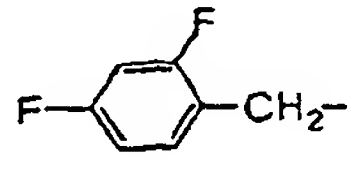
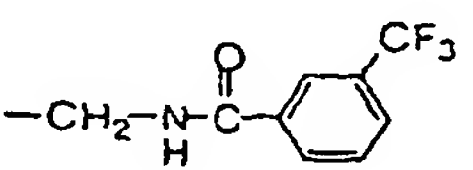
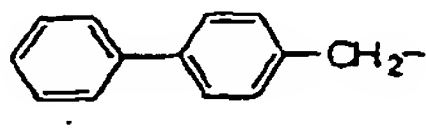
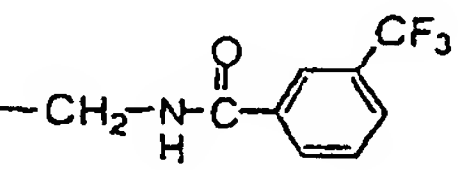
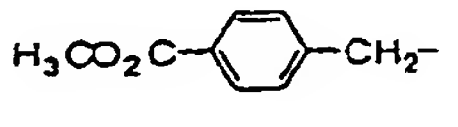
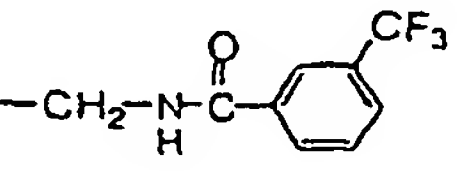
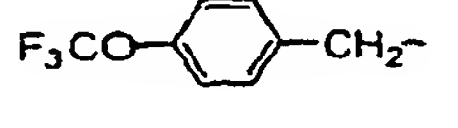
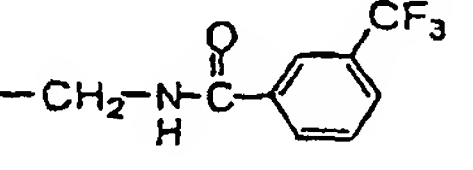
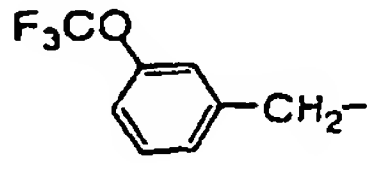
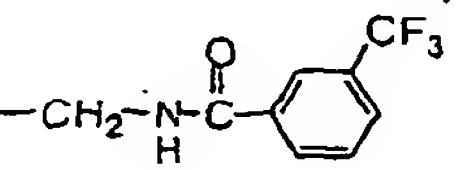
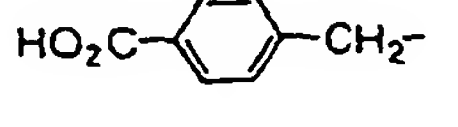
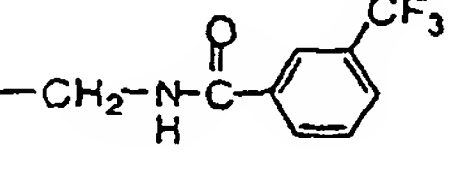
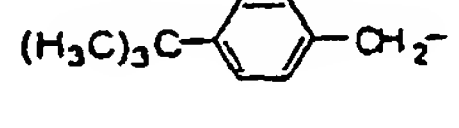
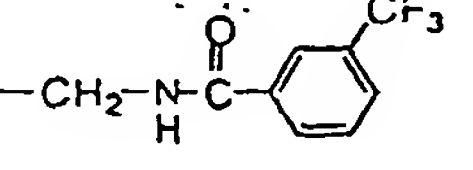
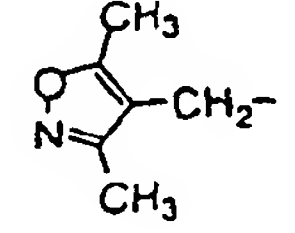
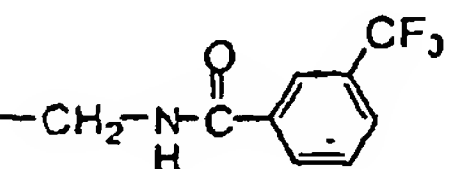
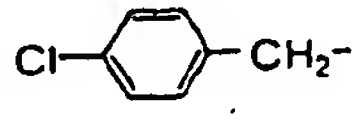
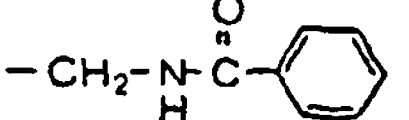
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
320		1	2	0	R	H	
321		1	2	0	R	H	
322		1	2	0	R	H	
323		1	2	0	R	H	
324		1	2	0	R	H	
325		1	2	0	R	H	
326		1	2	0	R	H	
327		1	2	0	R	H	
328		1	2	0	R	H	
329		1	2	0	R	H	
330		0	3	1	-	H	

Table 1.3 1

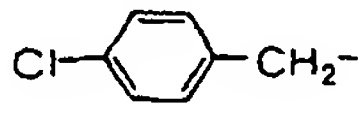
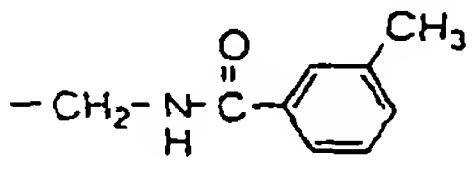
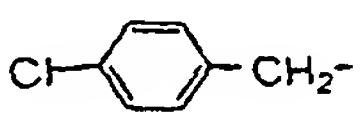
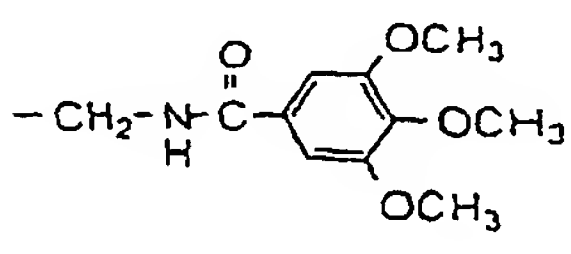
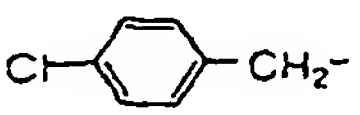
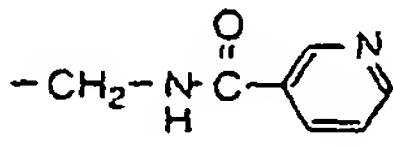
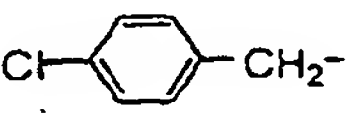
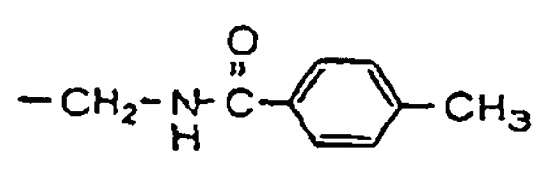
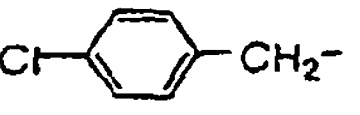
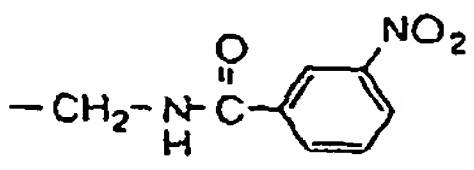
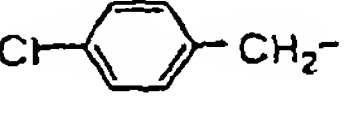
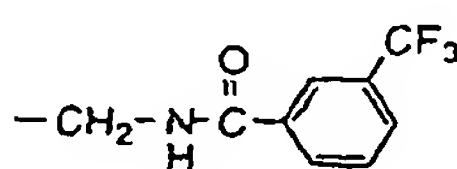
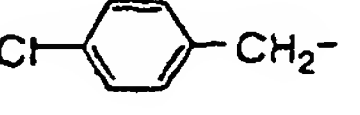
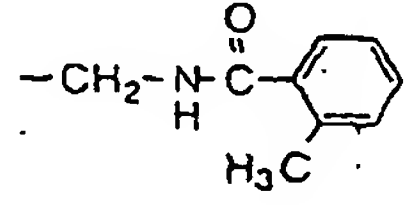
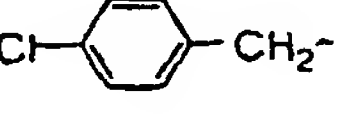
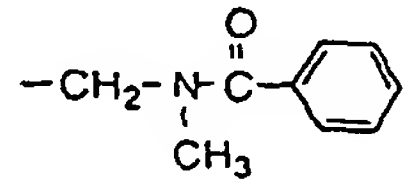
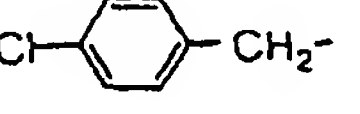
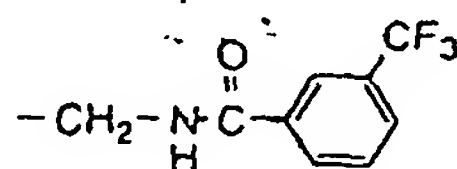
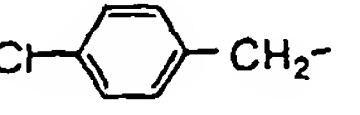
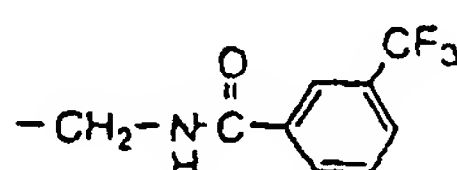
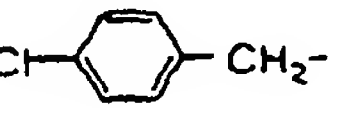
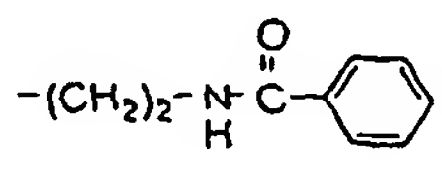
5 Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p-\overset{\overset{R^4}{ }}{\underset{\underset{R^5}{ }}{C}}-(CH_2)_q-G-R^6$
10 331		0	3	1	-	H	
15 332		0	3	1	-	H	
20 333		0	3	1	-	H	
25 334		0	3	1	-	H	
30 335		0	3	1	-	H	
35 336		0	3	1	-	H	
40 337		0	3	1	-	H	
45 338		0	3	1	-	H	
50 339		0	3	1	R	H	
55 340		0	3	1	S	H	
341		0	3	1	-	H	

Table 1.3 2

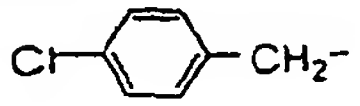
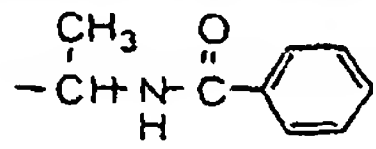
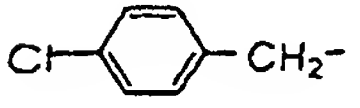
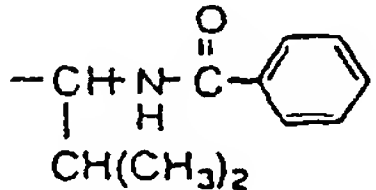
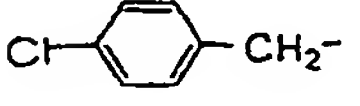
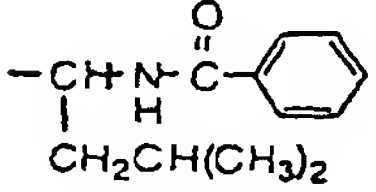
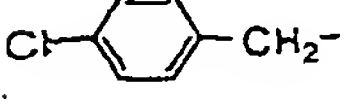
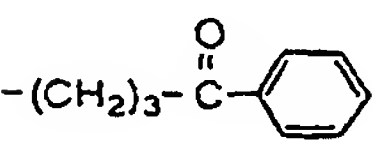
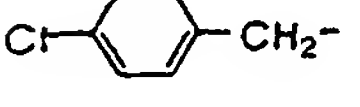
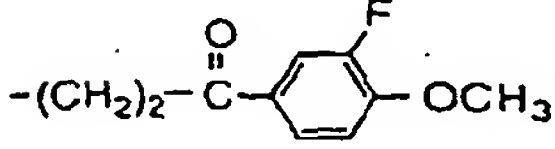
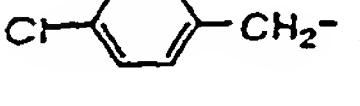
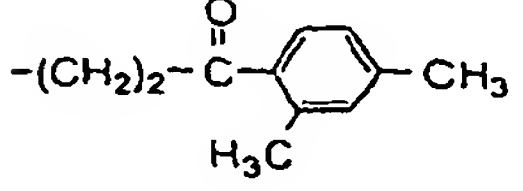
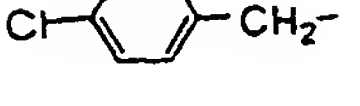
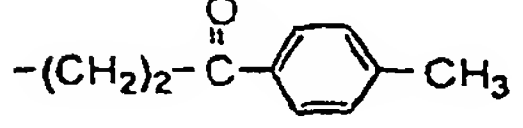
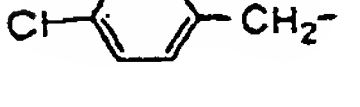
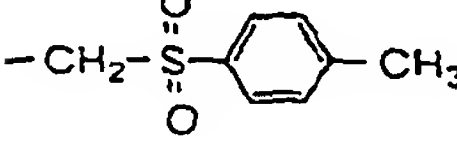
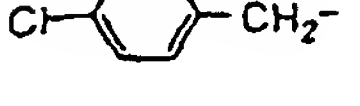
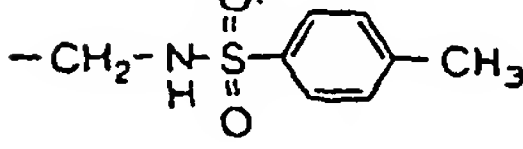
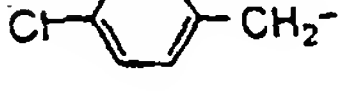
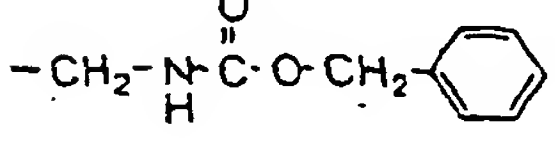
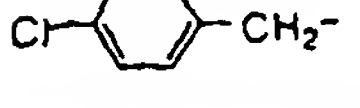
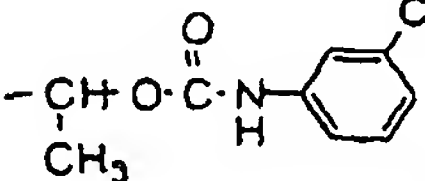
Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (CH_2)_j \text{---}$	k	m	n	chirality	R^3	$-(CH_2)_p \text{---} \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q \text{---} G \text{---} R^6$
342		0	3	1	-	H	
343		0	3	1	-	H	
344		0	3	1	-	H	
345		0	3	1	-	H	
346		0	3	1	-	H	
347		0	3	1	-	H	
348		0	3	1	-	H	
349		0	3	1	-	H	
350		0	3	1	-	H	
351		0	3	1	-	H	
352		0	3	1	-	H	

Table 1.33

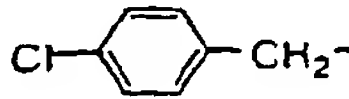
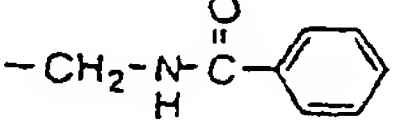

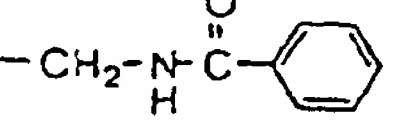
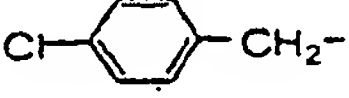
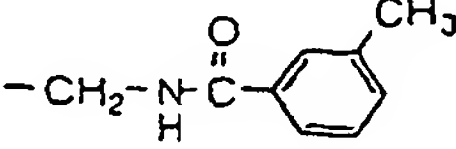
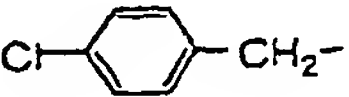
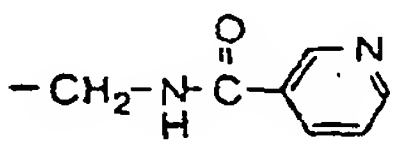
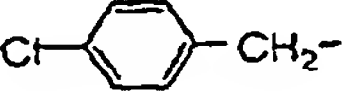
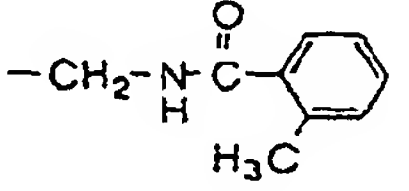
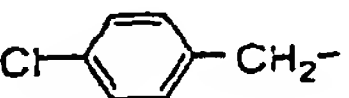
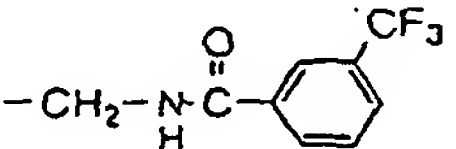
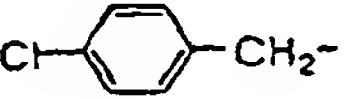
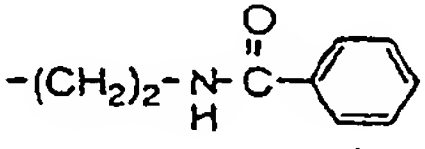

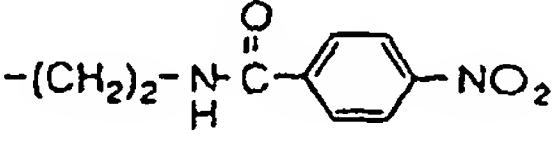

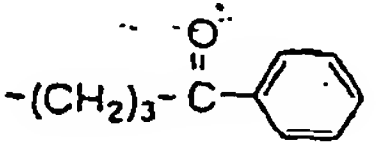
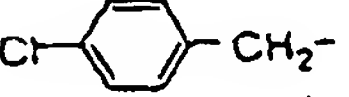
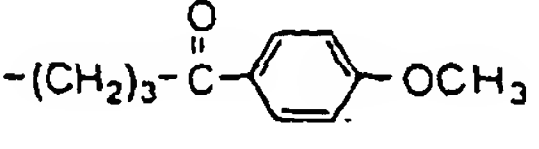
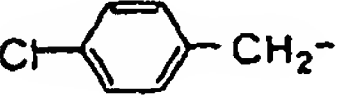
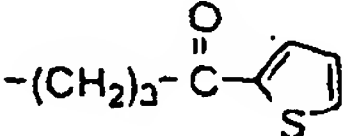
Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (CH_2)_j \text{---}$	k	m	n	chirality	R^3	$-(CH_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} \text{---} (CH_2)_q \text{---} G \text{---} R^6$
353		1	2	1	-	H	
354		1	3	0	-	H	
355		1	3	0	-	H	
356		1	3	0	-	H	
357		1	3	0	-	H	
358		1	3	0	-	H	
359		1	3	0	-	H	
360		1	3	0	-	H	
361		1	3	0	-	H	
362		1	3	0	-	H	
363		1	3	0	-	H	

Table 1.3 4

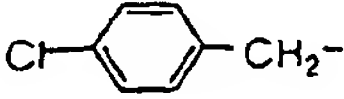
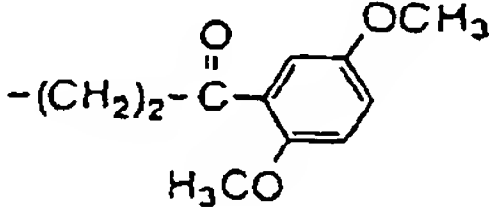
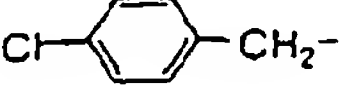
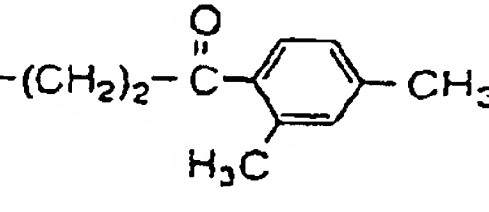
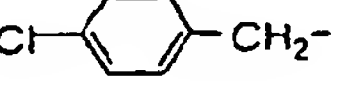
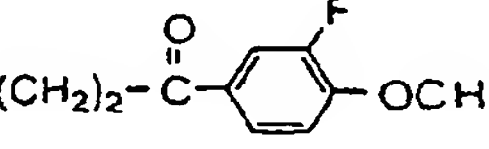
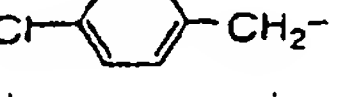
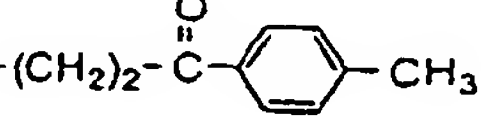
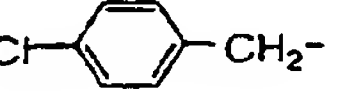
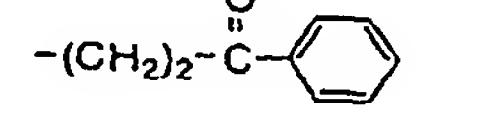
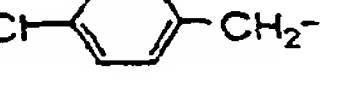
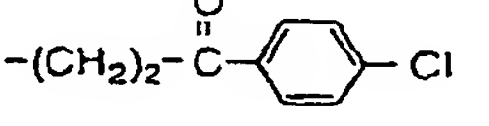
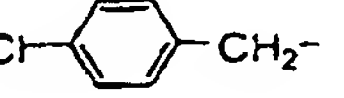
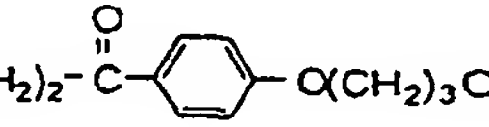
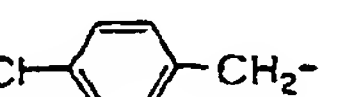
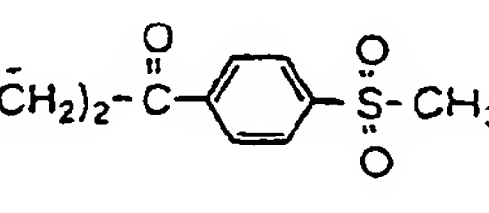
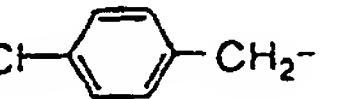
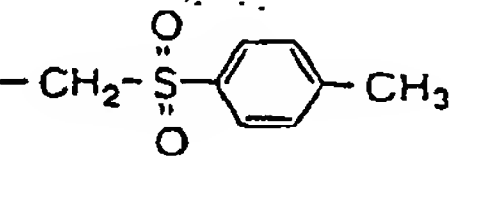
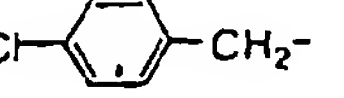
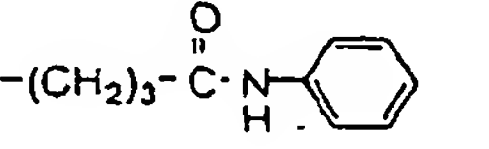
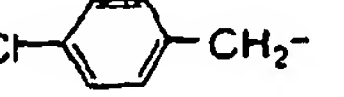
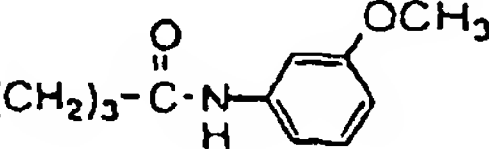
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_l \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
364		1	3	0	-	H	
365		1	3	0	-	H	
366		1	3	0	-	H	
367		1	3	0	-	H	
368		1	3	0	-	H	
369		1	3	0	-	H	
370		1	3	0	-	H	
371		1	3	0	-	H	
372		1	3	0	-	H	
373		1	3	0	-	H	
374		1	3	0	-	H	

Table 1.3 5

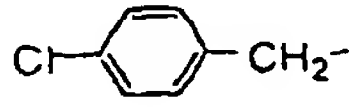
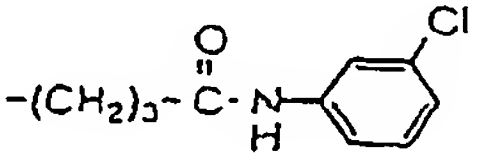
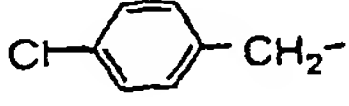
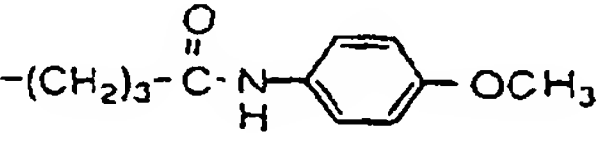
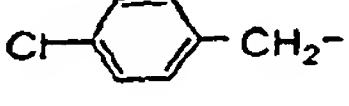
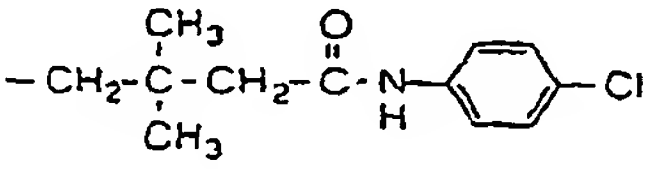
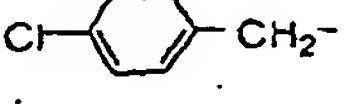
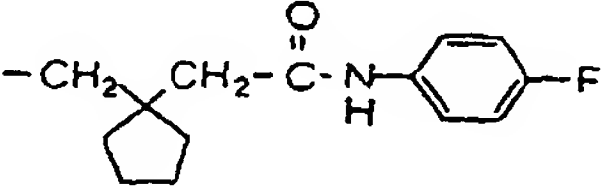

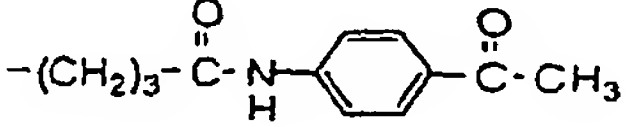

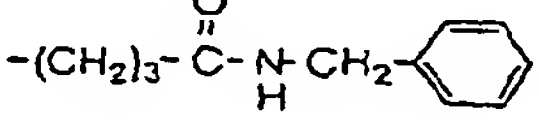
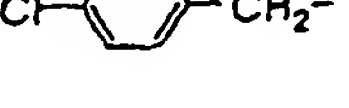
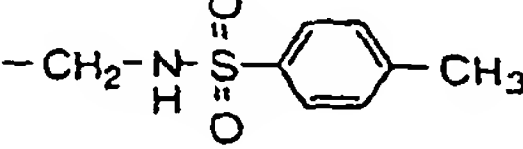

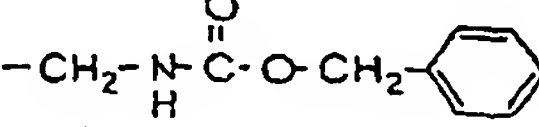
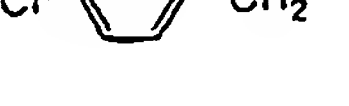
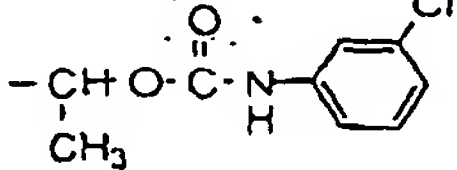

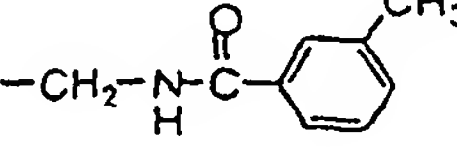

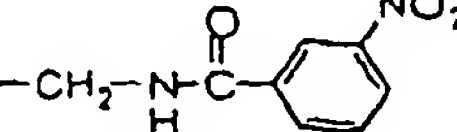
Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (\text{CH}_2)_j \text{---}$	k	m	n	chirality	R^3	$-(\text{CH}_2)_p \text{---} \begin{matrix} R^4 \\ \\ R^5 \end{matrix} \text{---} (\text{CH}_2)_q \text{---} \text{G---} R^6$
375		1	3	0	-	H	
376		1	3	0	-	H	
377		1	3	0	-	H	
378		1	3	0	-	H	
379		1	3	0	-	H	
380		1	3	0	-	H	
381		1	3	0	-	H	
382		1	3	0	-	H	
383		1	3	0	-	H	
384		2	2	0	-	H	
385		2	2	0	-	H	

Table 1.3.6


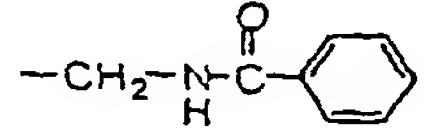

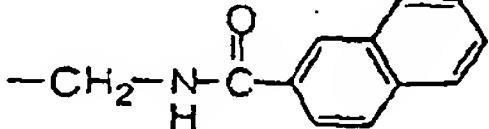

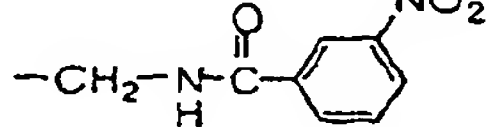
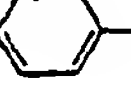
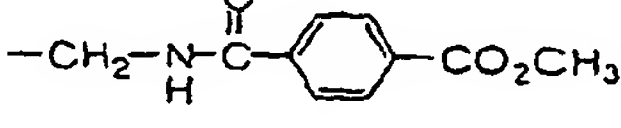

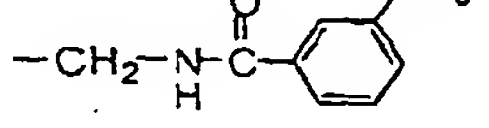
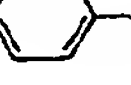
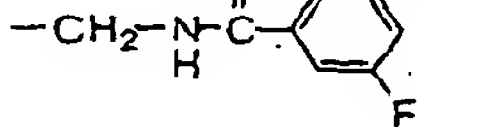

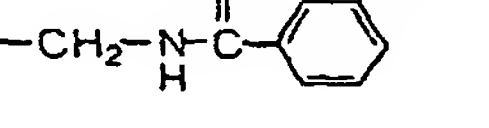

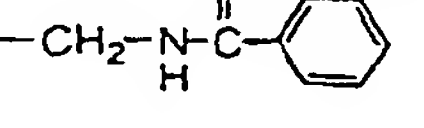

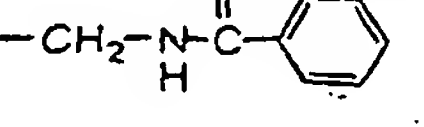
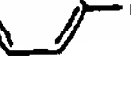
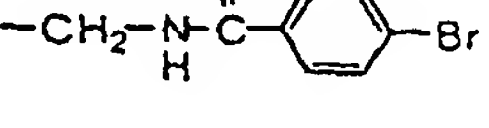

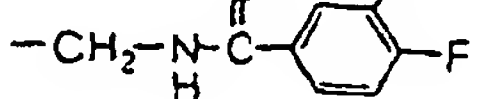
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
386	 -CH ₂ -	2	2	0	-	H	
387	 -CH ₂ -	2	2	0	-	H	
388	 -CH ₂ -	2	2	0	-	H	
389	 -CH ₂ -	2	2	0	-	H	
390	 -CH ₂ -	2	2	0	-	H	
391	 -CH ₂ -	2	2	0	-	H	
392	 -CH ₂ -	2	2	0	-	H	
393	 -CH ₂ -	2	2	0	-	H	
394	 -CH ₂ -	2	2	0	-	H	
395	 -CH ₂ -	2	2	0	-	H	
396	 -CH ₂ -	2	2	0	-	H	

Table 1.37

Compd. No.	$\begin{array}{c} R^1 \\ \\ R^2 - (CH_2)_j - \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p - \begin{array}{c} R^4 \\ \\ R^5 \end{array} - (CH_2)_q - G - R^6$
397		2	2	0	-	H	
398		2	2	0	-	H	
399		2	2	0	-	H	
400		2	2	0	-	H	
401		2	2	0	-	H	
402		2	2	0	-	H	
403		2	2	0	-	H	
404		2	2	0	-	H	
405		2	2	0	-	H	
406		2	2	0	-	H	
407		2	2	0	-	H	

Table 1.3 8












5 Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_k \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
10 408	 -CH ₂ -	2	2	0	-	H	$-(CH_2)_2-NH-C(=O)-\text{2,4-difluorophenyl}$
15 409	 -CH ₂ -	2	2	0	-	H	$-(CH_2)_2-NH-C(=O)-\text{2,4-dichlorophenyl}$
20 410	 -CH ₂ -	2	2	0	-	H	$-(S)-CH(CH_2CH(CH_3)_2)-NH-C(=O)-\text{phenyl}$
25 411	 -CH ₂ -	2	2	0	-	H	$-(S)-CH(CH_2CH(CH_3)_2)-NH-C(=O)-\text{naphthalen-1-yl}$
30 412	 -CH ₂ -	2	2	0	-	H	$-(S)-CH(CH_2CH(CH_3)_2)-NH-C(=O)-\text{3-nitrophenyl}$
35 413	 -CH ₂ -	2	2	0	-	H	$-(S)-CH(CH_2CH(CH_3)_2)-NH-C(=O)-\text{4-methoxycarbonylphenyl}$
40 414	 -CH ₂ -	2	2	0	-	H	$-(S)-CH(CH_2CH(CH_3)_2)-NH-C(=O)-\text{4-(trifluoromethyl)phenyl}$
45 415	 -CH ₂ -	2	2	0	-	H	$-(S)-CH(CH_2CH(CH_3)_2)-NH-C(=O)-\text{2-(trifluoromethyl)-4-fluorophenyl}$
50 416	 -CH ₂ -	2	2	0	-	H	$-(S)-CH(CH_2CH(CH_3)_2)-NH-C(=O)-\text{4-(trifluoromethoxy)phenyl}$
55 417	 -CH ₂ -	2	2	0	-	H	$-(S)-CH(CH_2CH(CH_3)_2)-NH-C(=O)-\text{3-bromophenyl}$
418	 -CH ₂ -	2	2	0	-	H	$-(S)-CH(CH_2CH(CH_3)_2)-NH-C(=O)-\text{4-chlorophenyl}$

Table 1.3 9

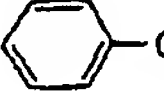
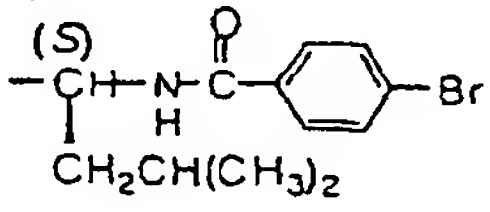

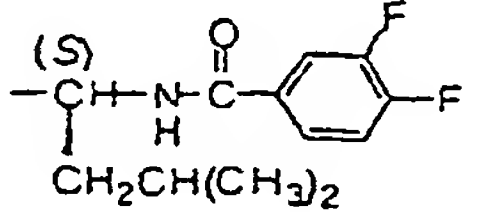
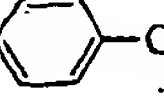
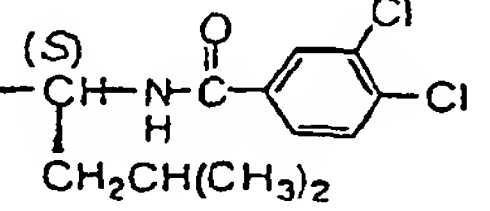

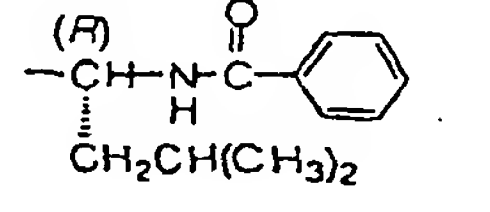
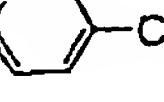
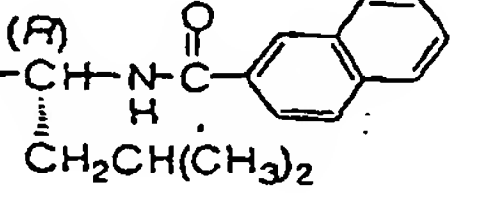
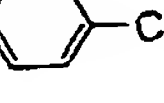
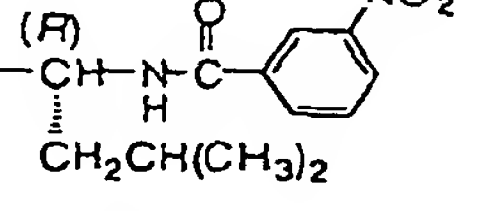

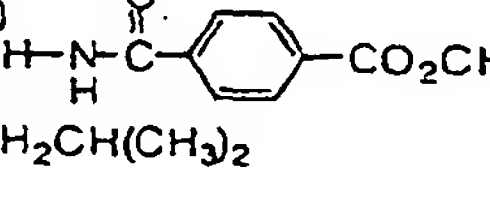
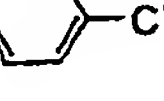
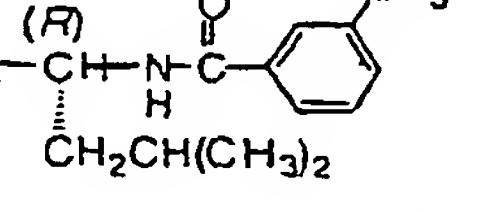
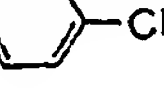
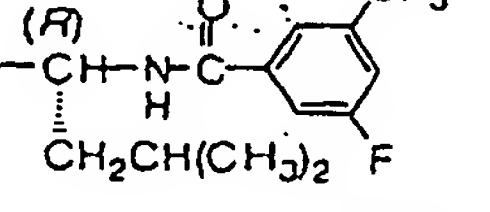
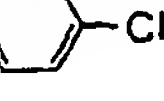
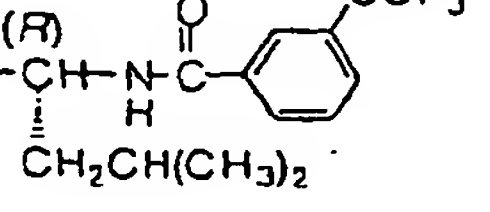
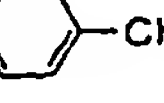
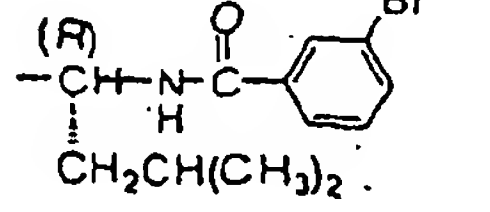
5 10 15 20 25 30 35 40 45 50 55	Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_i -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
	419.	 -CH ₂ -	2	2	0	-	H	
	420	 -CH ₂ -	2	2	0	-	H	
	421	 -CH ₂ -	2	2	0	-	H	
	422	 -CH ₂ -	2	2	0	-	H	
	423	 -CH ₂ -	2	2	0	-	H	
	424	 -CH ₂ -	2	2	0	-	H	
	425	 -CH ₂ -	2	2	0	-	H	
	426	 -CH ₂ -	2	2	0	-	H	
	427	 -CH ₂ -	2	2	0	-	H	
	428	 -CH ₂ -	2	2	0	-	H	
	429	 -CH ₂ -	2	2	0	-	H	

Table 1.4 0

5 10 15 20 25 30 35 40 45 50 55	Compd. No.	$\begin{array}{c} R^1 \\ \\ R^2 \end{array} (CH_2)_l$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
	430		2	2	0	-	H	
	431		2	2	0	-	H	
	432		2	2	0	-	H	
	433		2	2	0	-	H	
	434		1	3	1	-	H	
	435		1	3	1	-	H	
	436		1	3	1	-	H	
	437		1	3	1	-	H	
	438		1	3	1	-	H	
	439		1	3	1	-	H	
	440		1	3	1	-	H	

Table 1.4 1

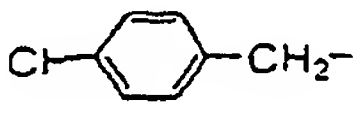
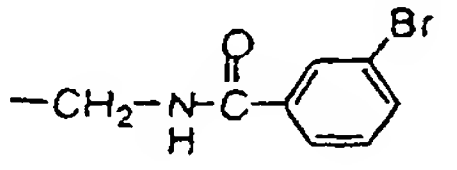
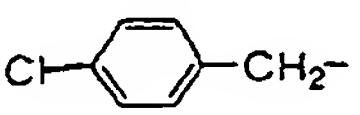
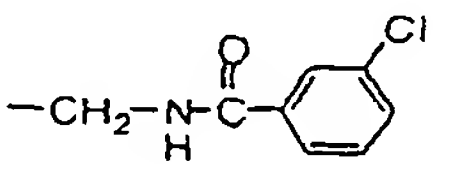
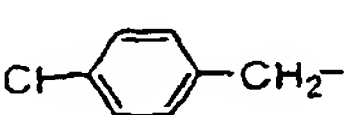
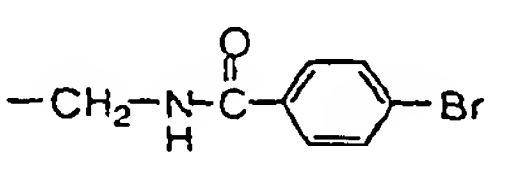
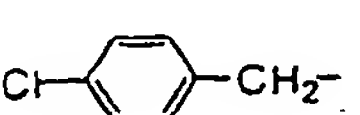
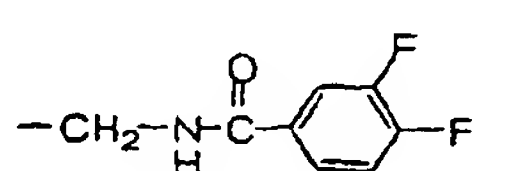
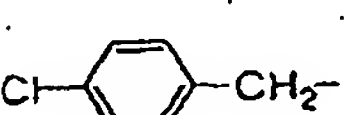
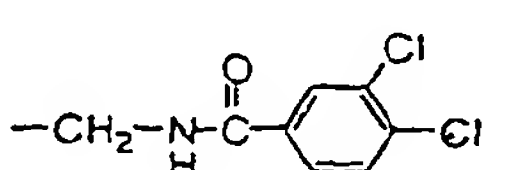
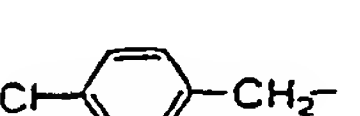
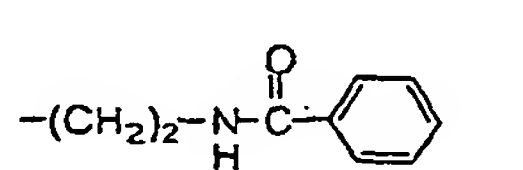
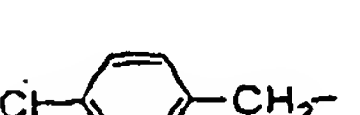
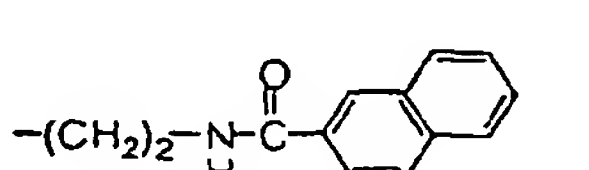

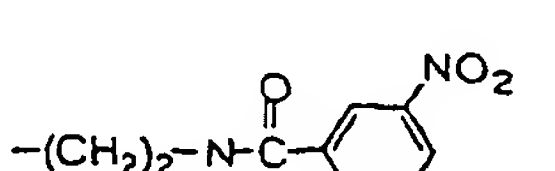

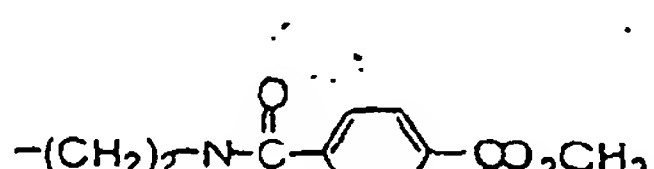



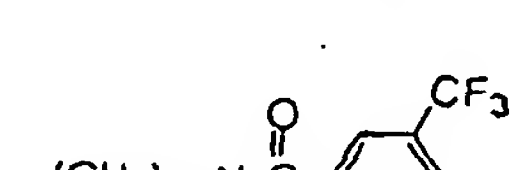
Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ (CH_2)_k \\ \diagdown \\ R^2 \end{matrix}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ (CH_2)_q \\ \\ R^5 \end{matrix} -G-R^6$
441		1	3	1	-	H	
442		1	3	1	-	H	
443		1	3	1	-	H	
444		1	3	1	-	H	
445		1	3	1	-	H	
446		1	3	1	-	H	
447		1	3	1	-	H	
448		1	3	1	-	H	
449		1	3	1	-	H	
450		1	3	1	-	H	
451		1	3	1	-	H	

Table 1.42


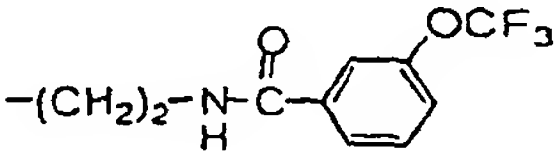
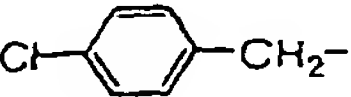
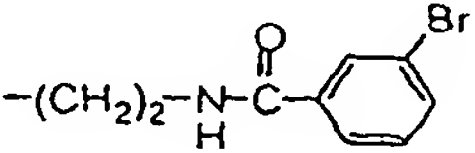
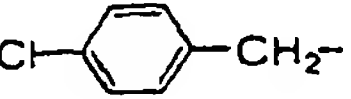
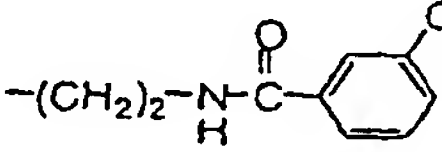
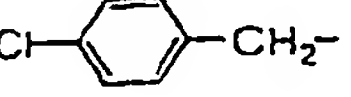
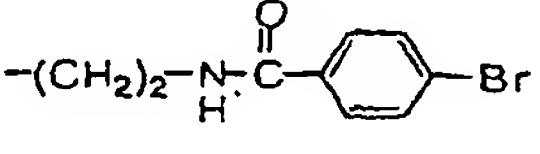

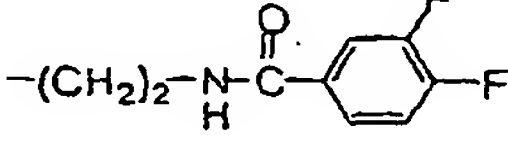
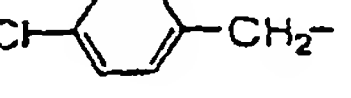
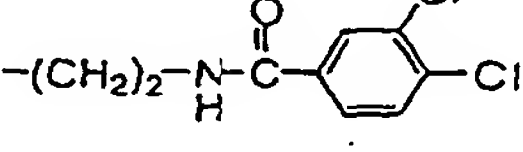
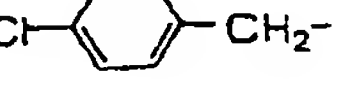
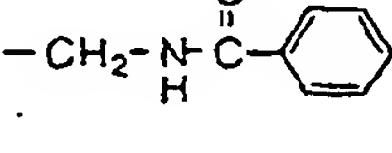
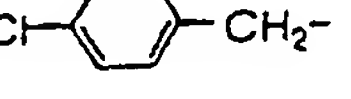
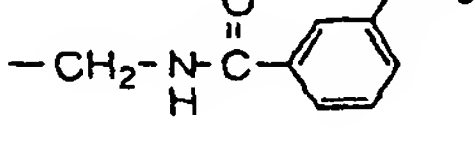
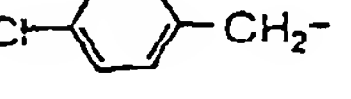
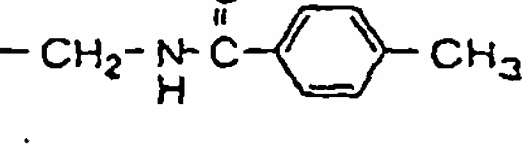
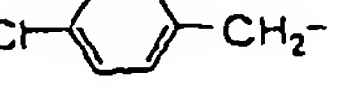
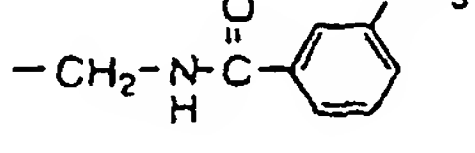
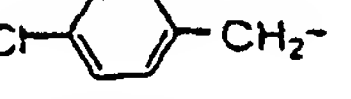
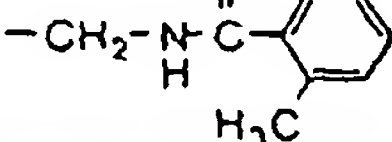
Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (CH_2)_j \text{---}$	k	m	n	chirality	R^3	$-(CH_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} \text{---} (CH_2)_q \text{---} G \text{---} R^6$
452		1	3	1	-	H	
453		1	3	1	-	H	
454		1	3	1	-	H	
455		1	3	1	-	H	
456		1	3	1	-	H	
457		1	3	1	-	H	
458		2	2	1	-	H	
459		2	2	1	-	H	
460		2	2	1	-	H	
461		2	2	1	-	H	
462		2	2	1	-	H	

Table 1.4 3

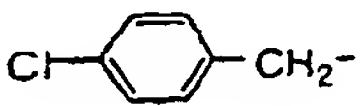
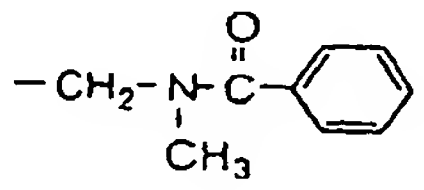
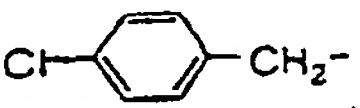
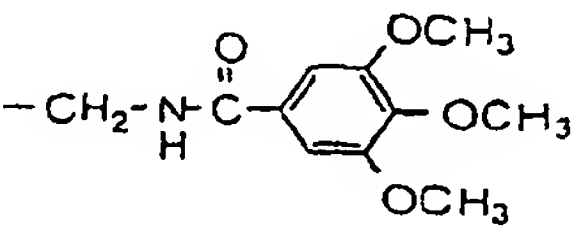
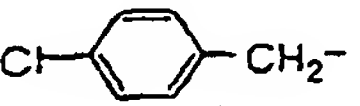
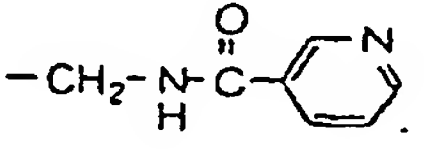
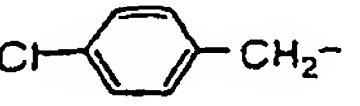
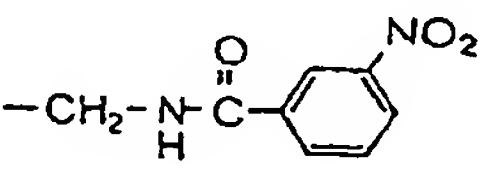

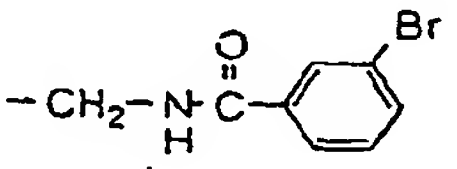

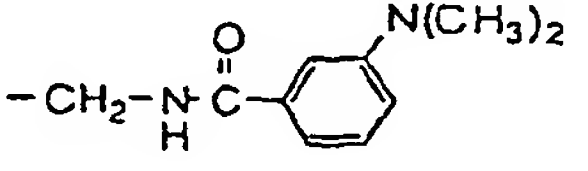
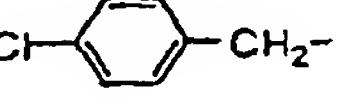
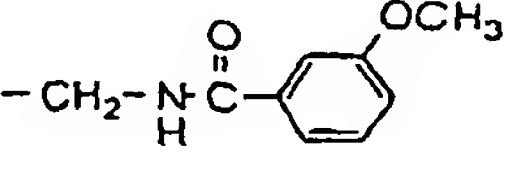
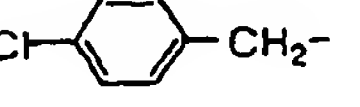
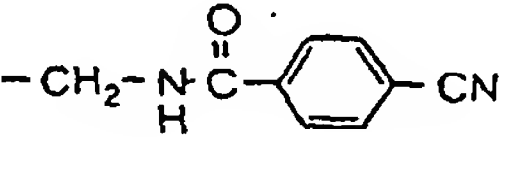
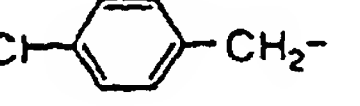
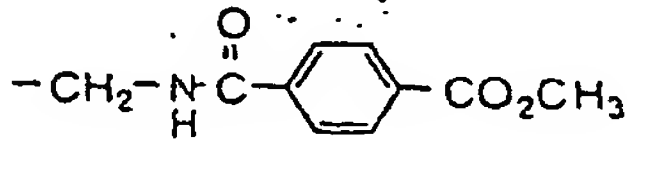
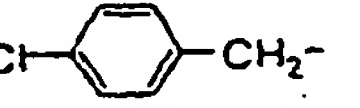
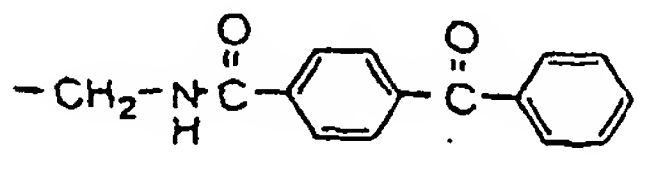
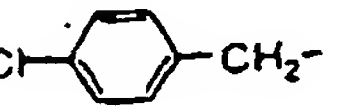
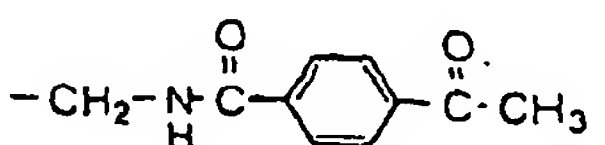
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_k \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
463		2	2	1	-	H	
464		2	2	1	-	H	
465		2	2	1	-	H	
466		2	2	1	-	H	
467		2	2	1	-	H	
468		2	2	1	-	H	
469		2	2	1	-	H	
470		2	2	1	-	H	
471		2	2	1	-	H	
472		2	2	1	-	H	
473		2	2	1	-	H	

Table 1.44

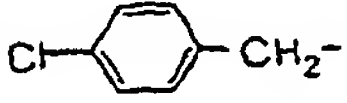
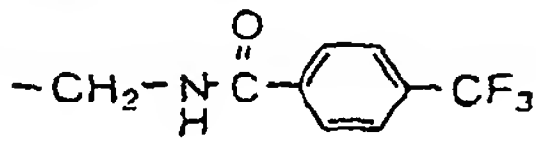
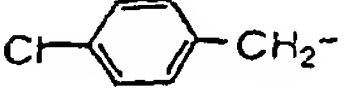
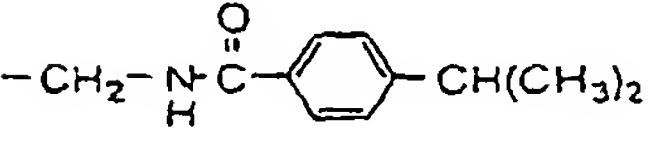

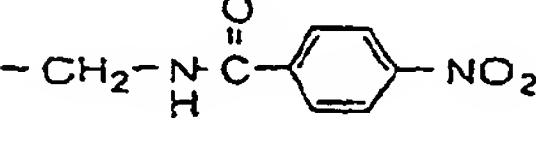
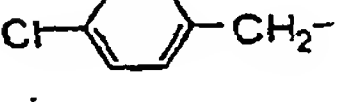
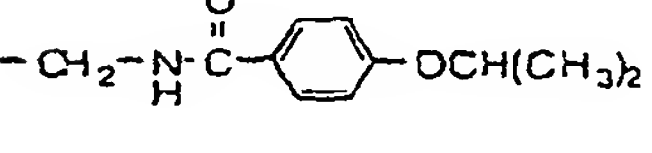

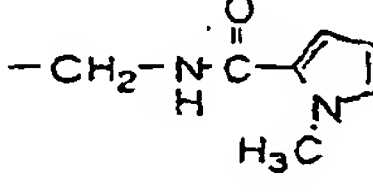

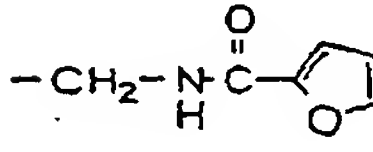

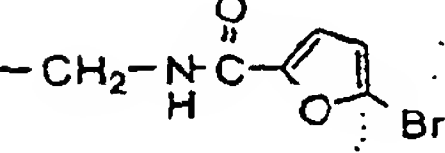

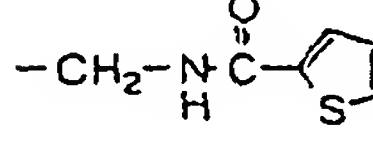
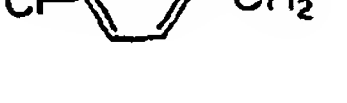
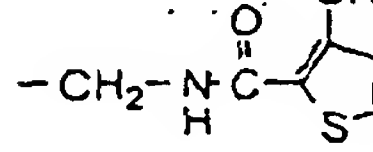
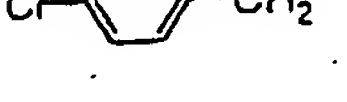
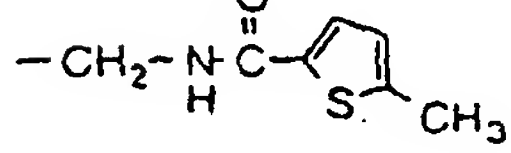

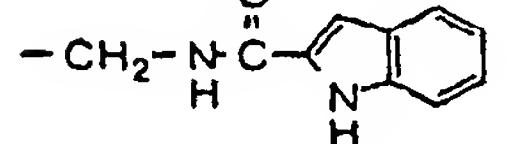
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p-\overset{\overset{R^4}{ }}{\underset{\underset{R^5}{ }}{C}}-(CH_2)_q-G-R^6$
474		2	2	1	-	H	
475		2	2	1	-	H	
476		2	2	1	-	H	
477		2	2	1	-	H	
478		2	2	1	-	H	
479		2	2	1	-	H	
480		2	2	1	-	H	
481		2	2	1	-	H	
482		2	2	1	-	H	
483		2	2	1	-	H	
484		2	2	1	-	H	

Table 1.45


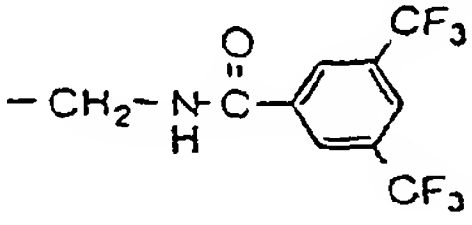

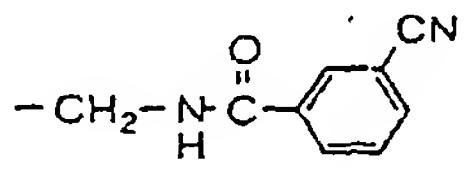
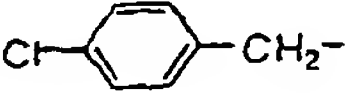
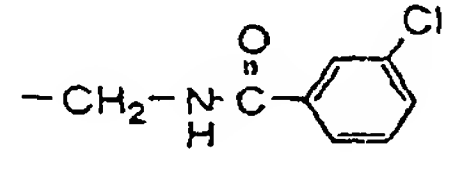

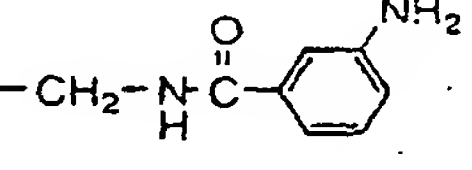

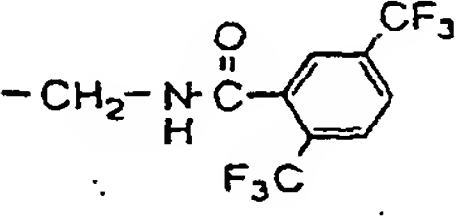

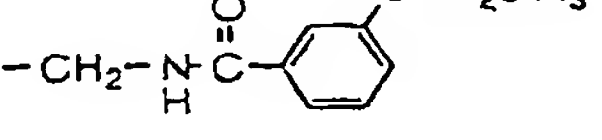

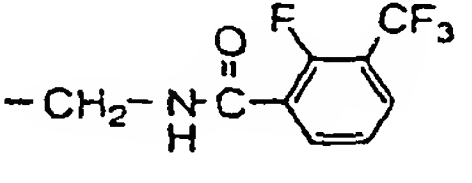
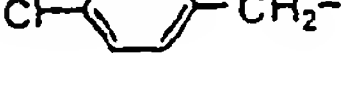
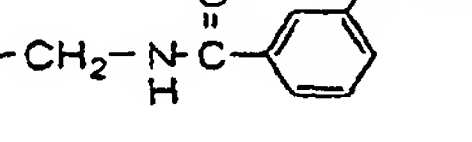

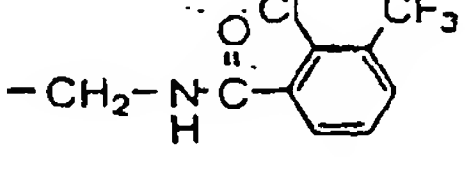

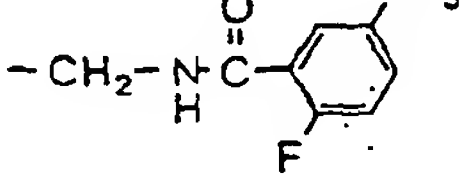

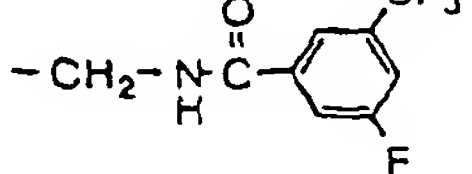
5	Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (\text{CH}_2)_l \text{---}$	k	m	n	chirality	R^3	$-(\text{CH}_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} \text{---} (\text{CH}_2)_q \text{---} G \text{---} R^6$
10	485		2	2	1	-	H	
15	486		2	2	1	-	H	
20	487		2	2	1	-	H	
25	488		2	2	1	-	H	
30	489		2	2	1	-	H	
35	490		2	2	1	-	H	
40	491		2	2	1	-	H	
45	492		2	2	1	-	H	
50	493		2	2	1	-	H	
55	494		2	2	1	-	H	
	495		2	2	1	-	H	

Table 1.46

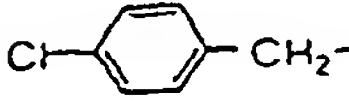
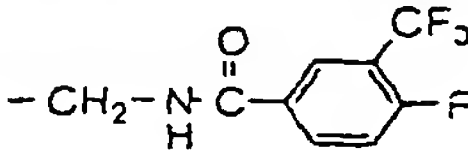
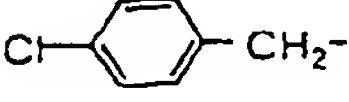
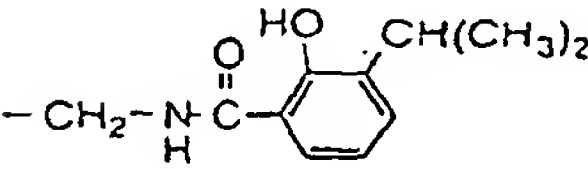
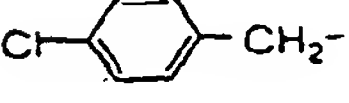
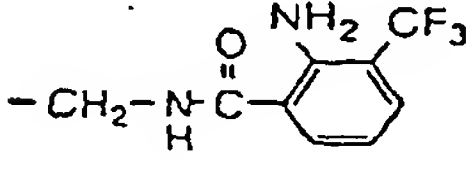
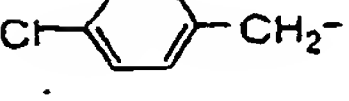
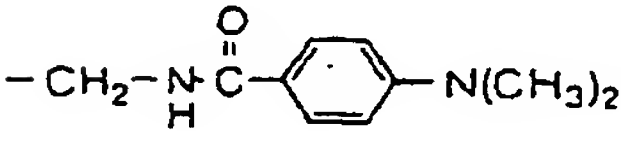
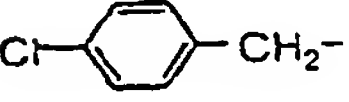
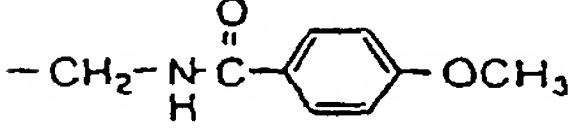
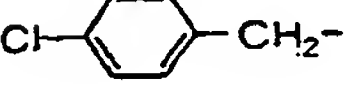
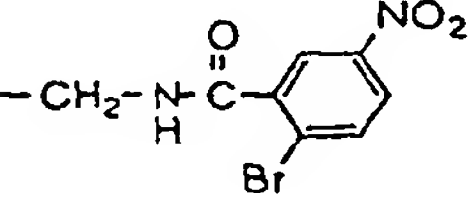
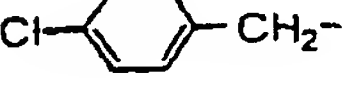
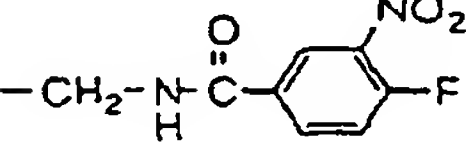
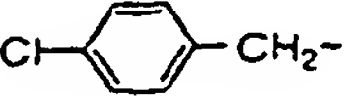
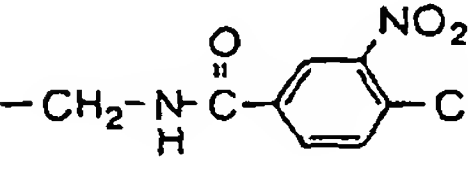
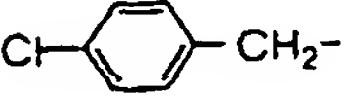
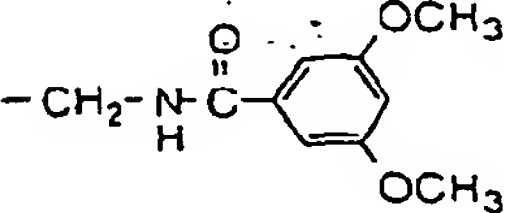
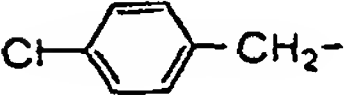
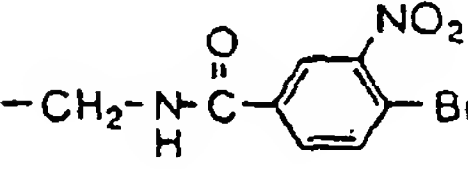
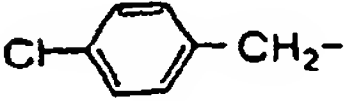
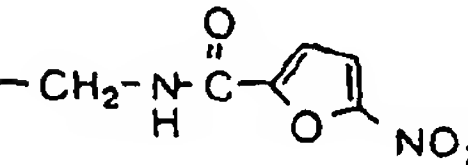
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_k \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
496		2	2	1	-	H	
497		2	2	1	-	H	
498		2	2	1	-	H	
499		2	2	1	-	H	
500		2	2	1	-	H	
501		2	2	1	-	H	
502		2	2	1	-	H	
503		2	2	1	-	H	
504		2	2	1	-	H	
505		2	2	1	-	H	
506		2	2	1	-	H	

Table 1.47


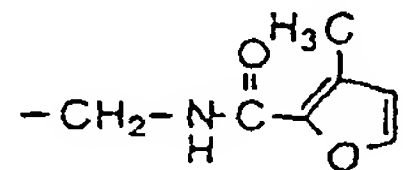
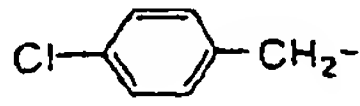
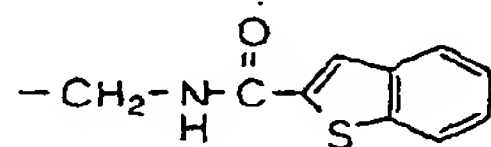
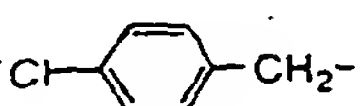
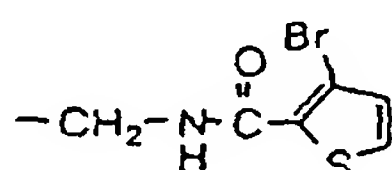
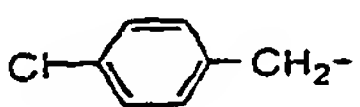
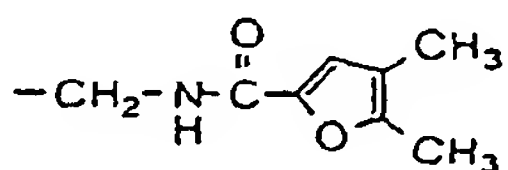
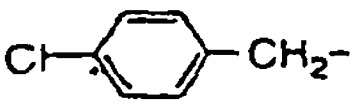
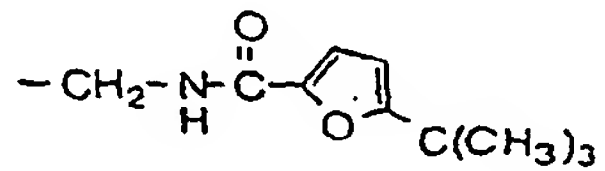
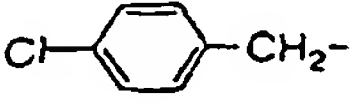
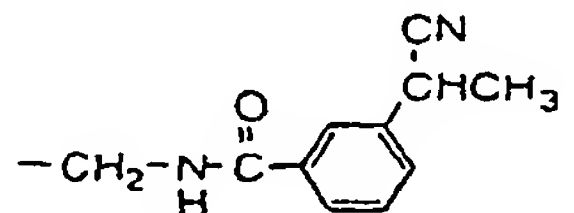

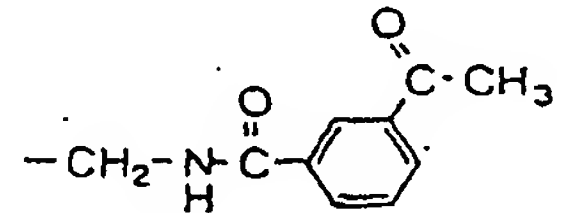
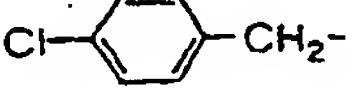
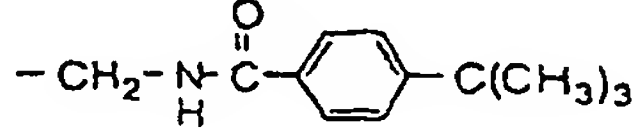
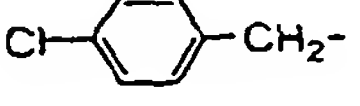
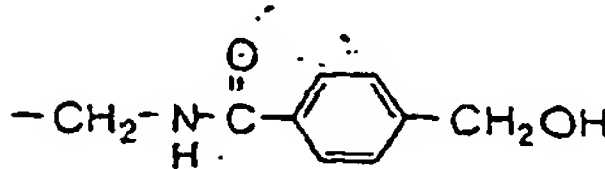
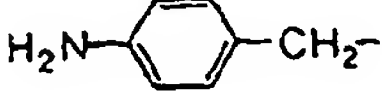
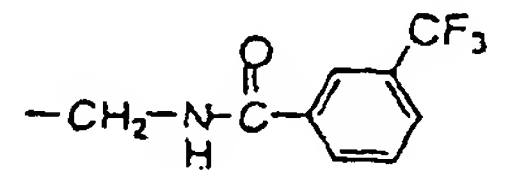
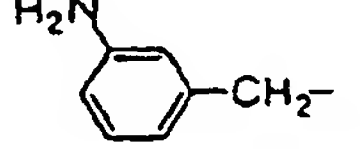
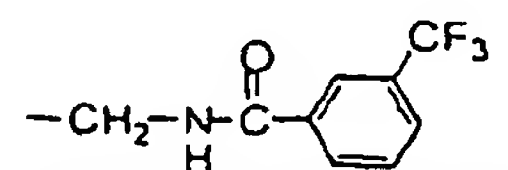
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
507		2	2	1	-	H	
508		2	2	1	-	H	
509		2	2	1	-	H	
510		2	2	1	-	H	
511		2	2	1	-	H	
512		2	2	1	-	H	
513		2	2	1	-	H	
514		2	2	1	-	H	
515		2	2	1	-	H	
516		2	2	1	-	H	
517		2	2	1	-	H	

Table 1.48

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
518		2	2	1	-	H	
519		2	2	1	-	H	
520		2	2	1	-	-CH ₃	
521		2	2	1	-		
522		2	2	1	-		
523		2	2	1	-		
524		2	2	1	-		
525		2	2	1	-	H	
526		2	2	1	-	H	
527		2	2	1	-	H	
528		2	2	1	-	H	

Table 1.4 9

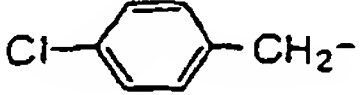
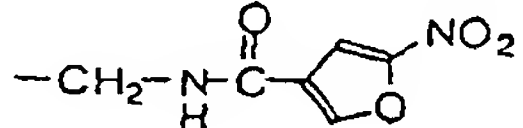

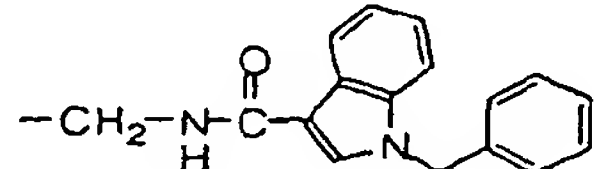
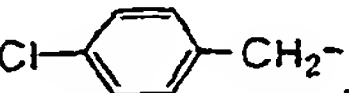
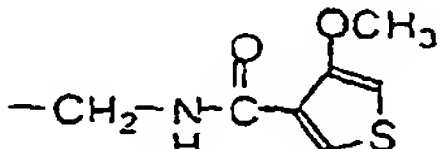
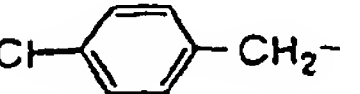
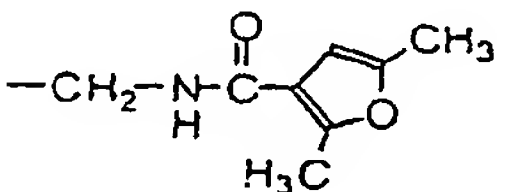

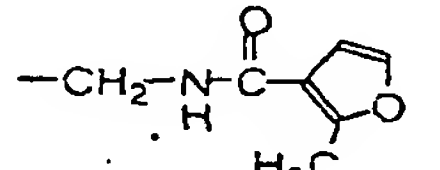
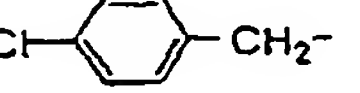
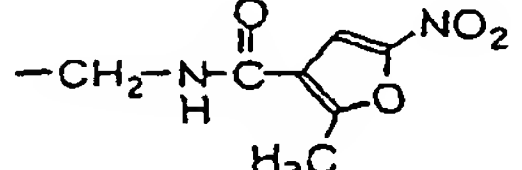
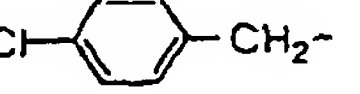
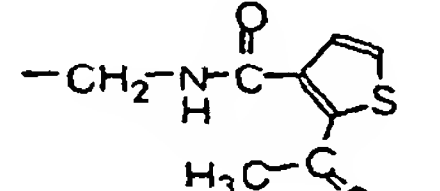
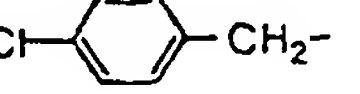
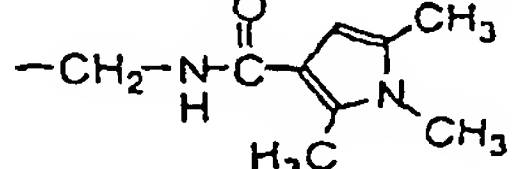
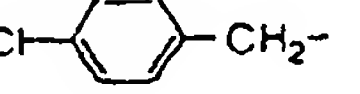
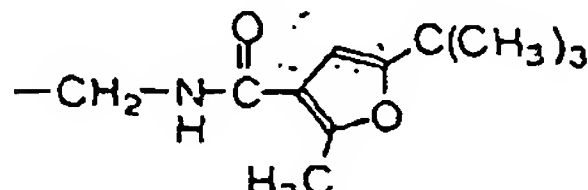
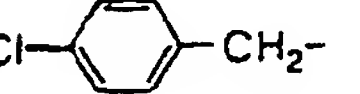
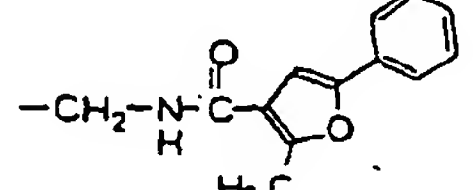
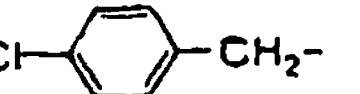
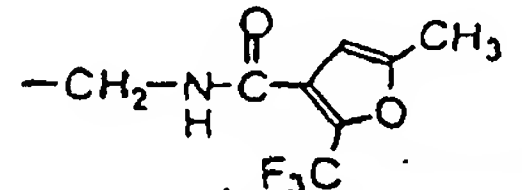
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_i$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
529		2	2	1	-	H	
530		2	2	1	-	H	
531		2	2	1	-	H	
532		2	2	1	-	H	
533		2	2	1	-	H	
534		2	2	1	-	H	
535		2	2	1	-	H	
536		2	2	1	-	H	
537		2	2	1	-	H	
538		2	2	1	-	H	
539		2	2	1	-	H	

Table 1.50


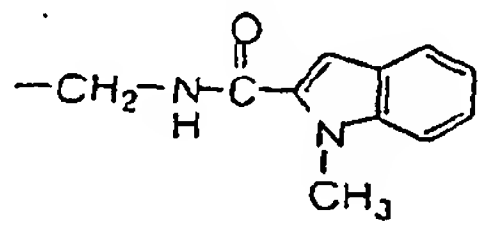

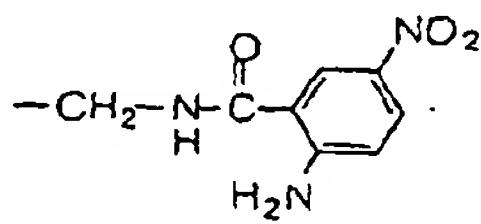

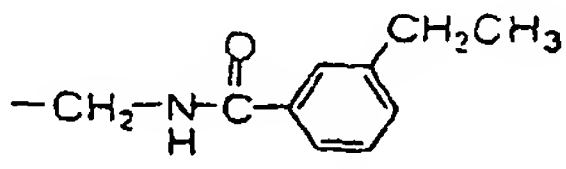

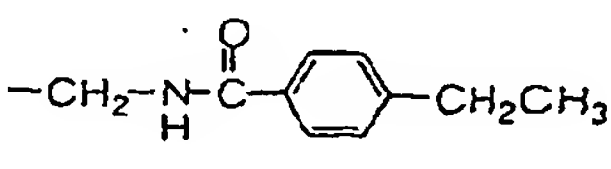
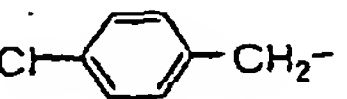
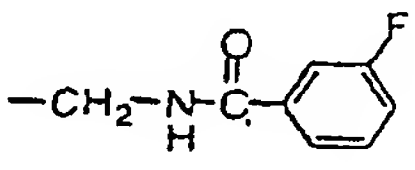
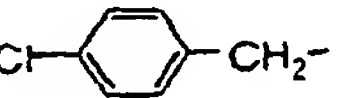
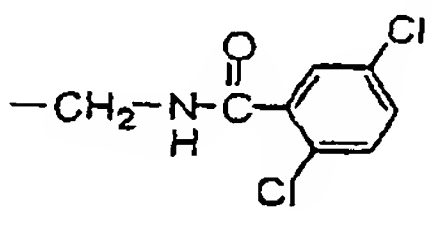

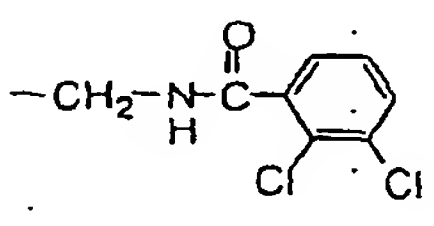
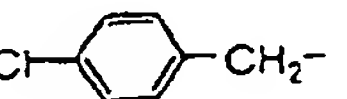
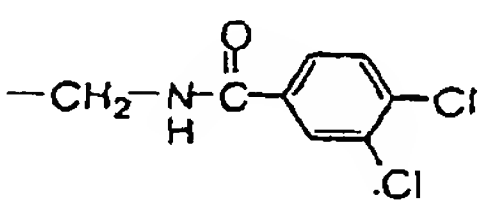
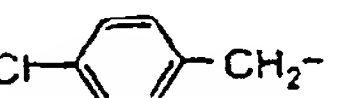
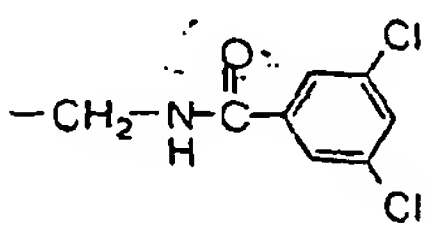

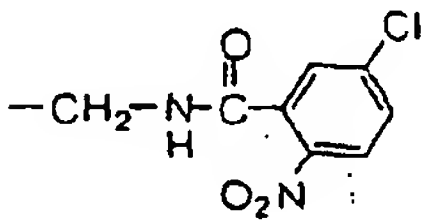
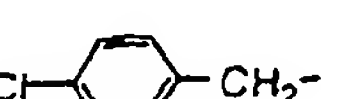
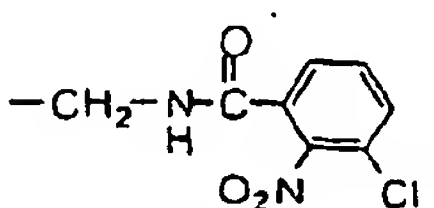
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q G-R^6$
540		2	2	1	-	H	
541		2	2	1	-	H	
542		2	2	1	-	H	
543		2	2	1	-	H	
544		2	2	1	-	H	
545		2	2	1	-	H	
546		2	2	1	-	H	
547		2	2	1	-	H	
548		2	2	1	-	H	
549		2	2	1	-	H	
550		2	2	1	-	H	

Table 1.5 1


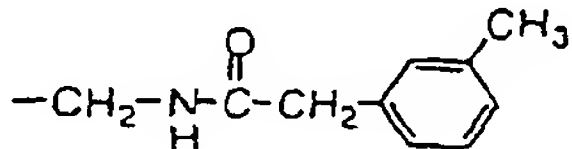
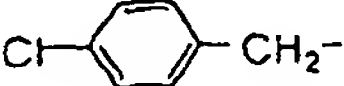
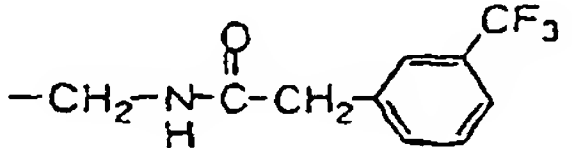

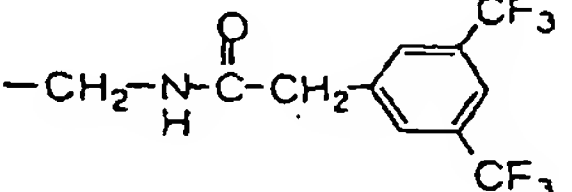
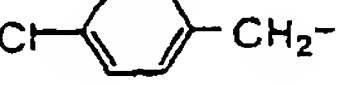
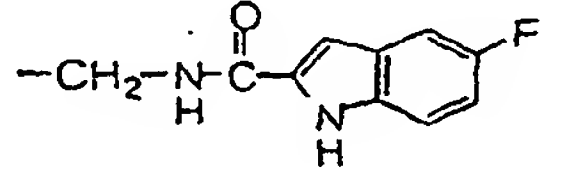
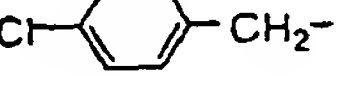
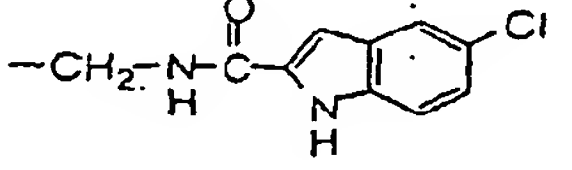

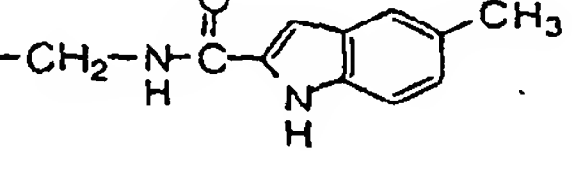

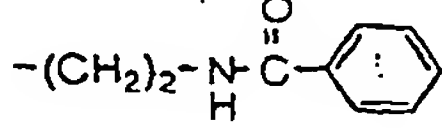
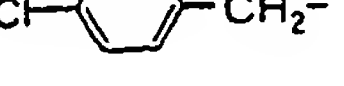
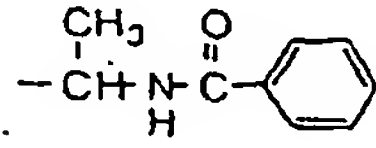

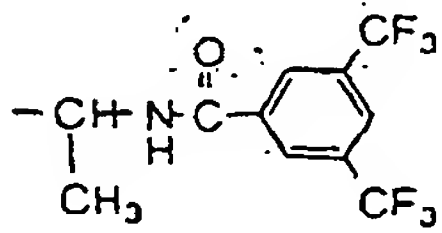

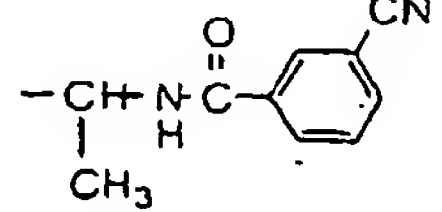

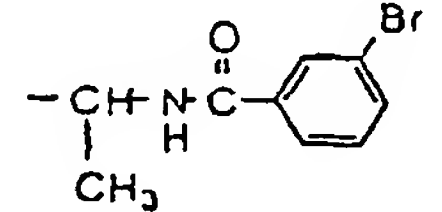
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_l \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
551		2	2	1	-	H	
552		2	2	1	-	H	
553		2	2	1	-	H	
554		2	2	1	-	H	
555		2	2	1	-	H	
556		2	2	1	-	H	
557		2	2	1	-	H	
558		2	2	1	-	H	
559		2	2	1	-	H	
560		2	2	1	-	H	
561		2	2	1	-	H	

Table 1.5 2

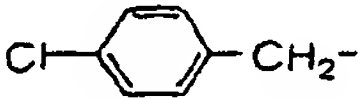
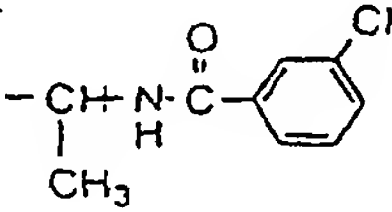
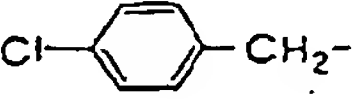
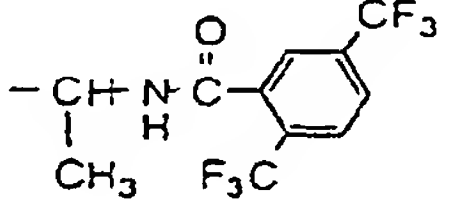
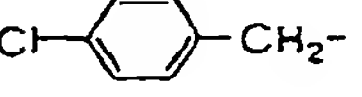
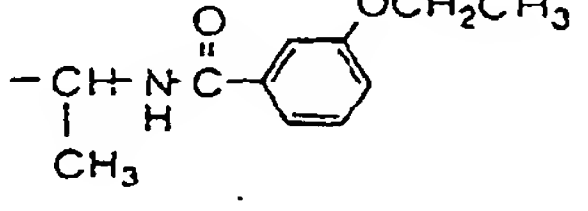
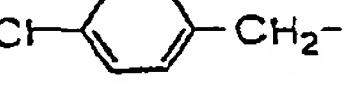
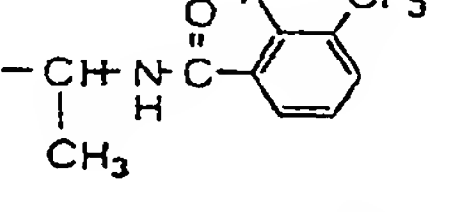
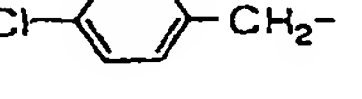
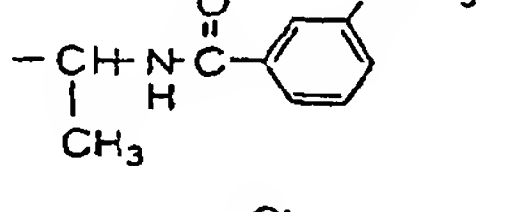
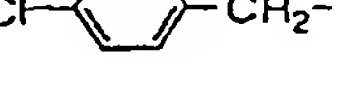
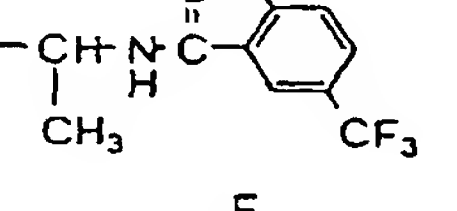

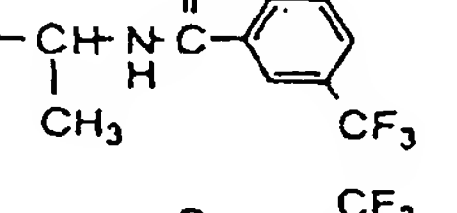

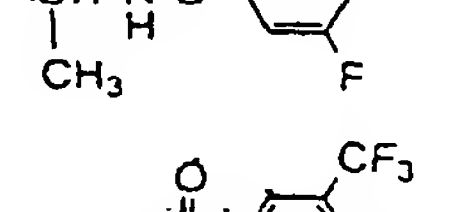

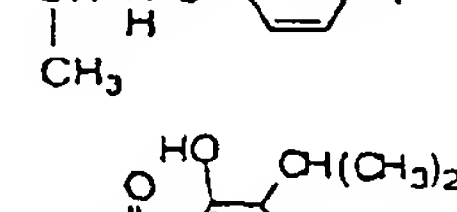

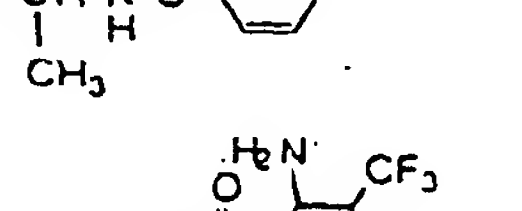

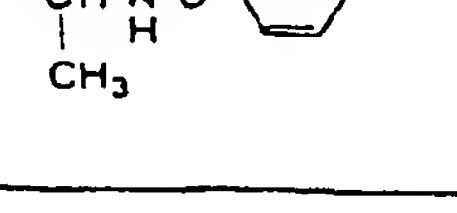
Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ R^2 \end{matrix} (CH_2)_j$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
562		2	2	1	-	H	
563		2	2	1	-	H	
564		2	2	1	-	H	
565		2	2	1	-	H	
566		2	2	1	-	H	
567		2	2	1	-	H	
568		2	2	1	-	H	
569		2	2	1	-	H	
570		2	2	1	-	H	
571		2	2	1	-	H	
572		2	2	1	-	H	

Table 1.53

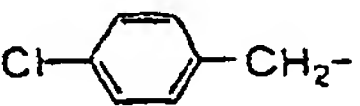
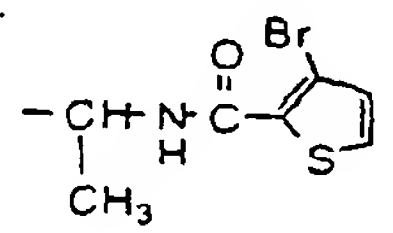
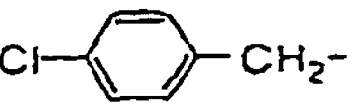
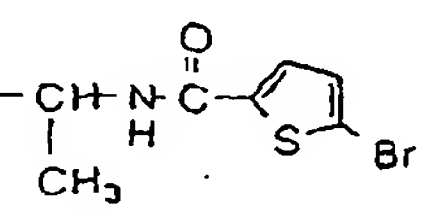

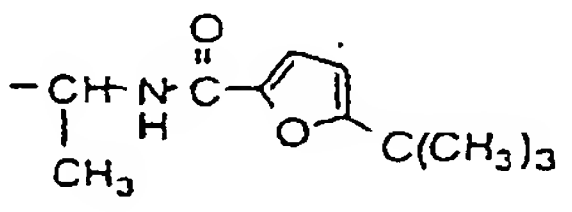
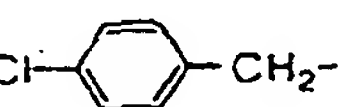
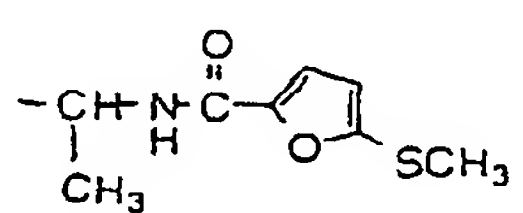
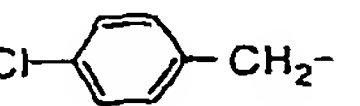
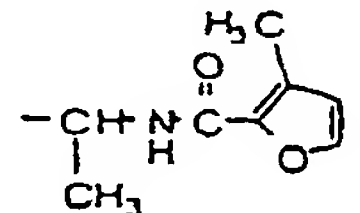
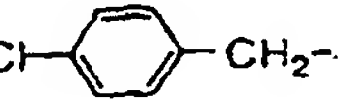
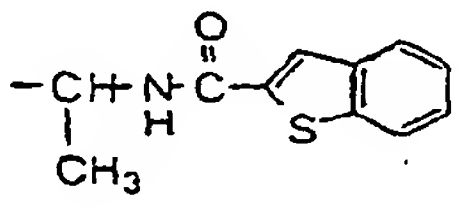
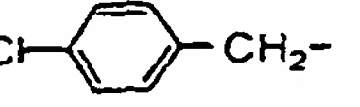
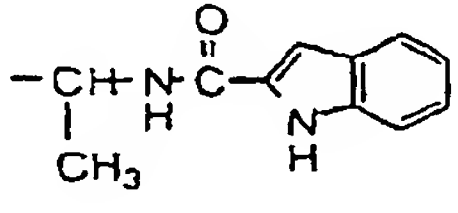
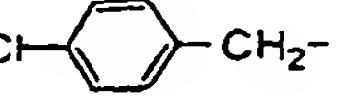
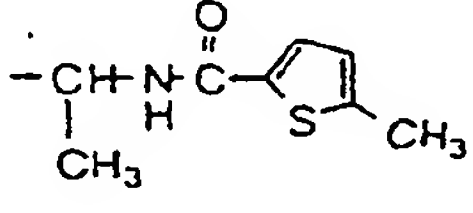
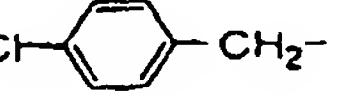
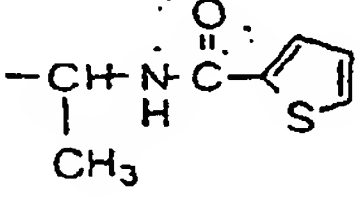
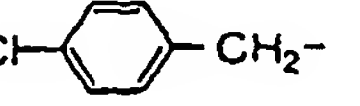
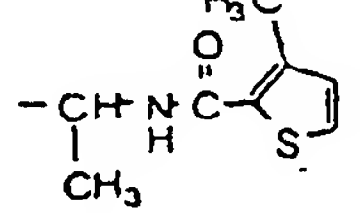
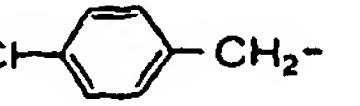
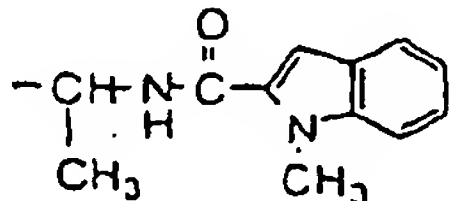
Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ (CH_2)_k \\ \diagdown \\ R^2 \end{matrix}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
573		2	2	1	-	H	
574		2	2	1	-	H	
575		2	2	1	-	H	
576		2	2	1	-	H	
577		2	2	1	-	H	
578		2	2	1	-	H	
579		2	2	1	-	H	
580		2	2	1	-	H	
581		2	2	1	-	H	
582		2	2	1	-	H	
583		2	2	1	-	H	

Table 1.5 4

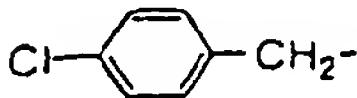
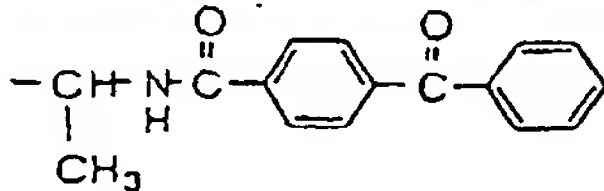
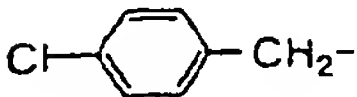
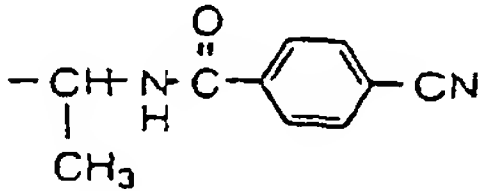
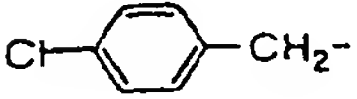
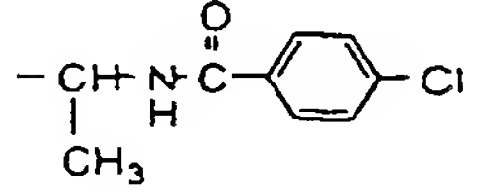
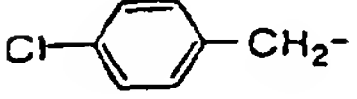
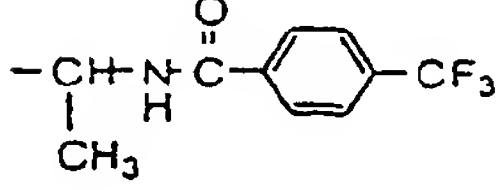
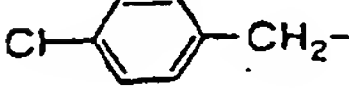
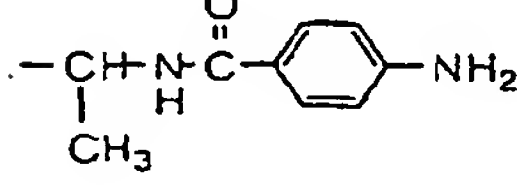
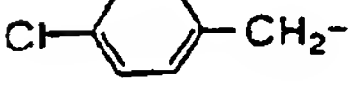
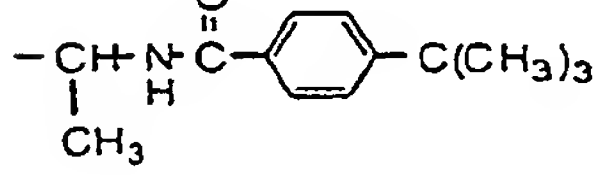
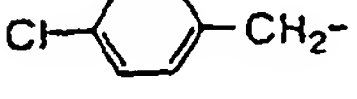
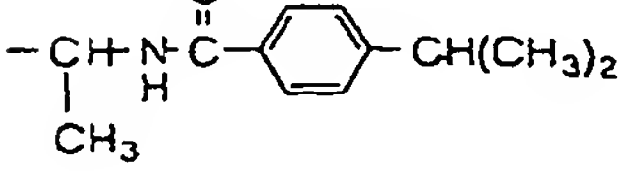
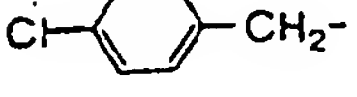
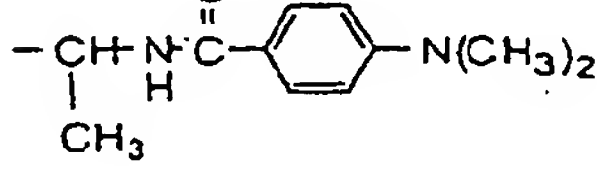

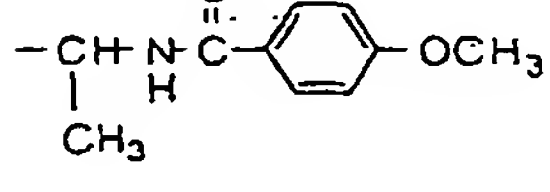
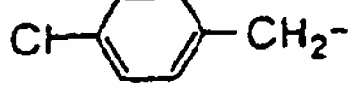
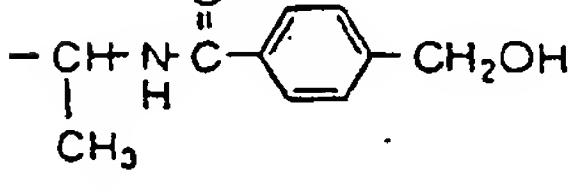
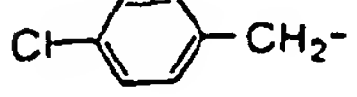
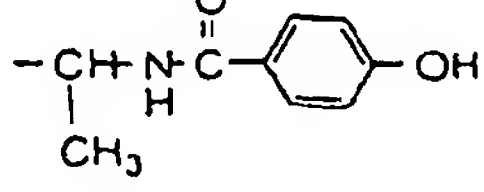
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_k \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q G-R^6$
584		2	2	1	-	H	
585		2	2	1	-	H	
586		2	2	1	-	H	
587		2	2	1	-	H	
588		2	2	1	-	H	
589		2	2	1	-	H	
590		2	2	1	-	H	
591		2	2	1	-	H	
592		2	2	1	-	H	
593		2	2	1	-	H	
594		2	2	1	-	H	

Table 1.5 5

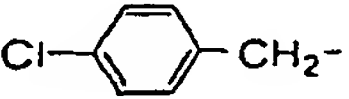
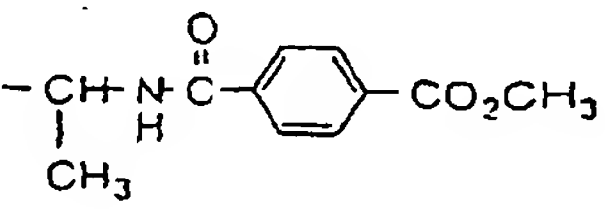
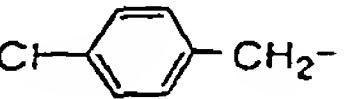
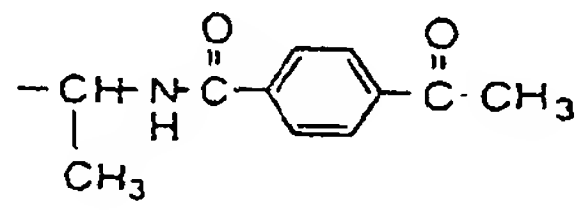
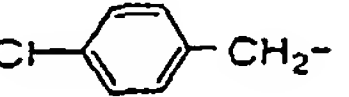
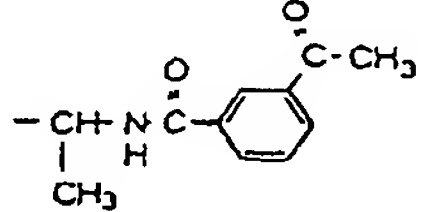
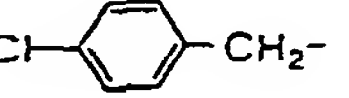
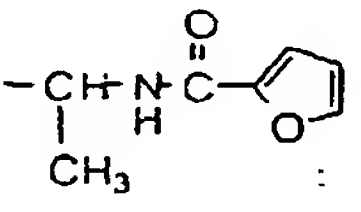
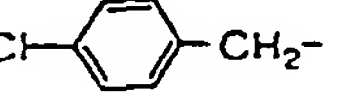
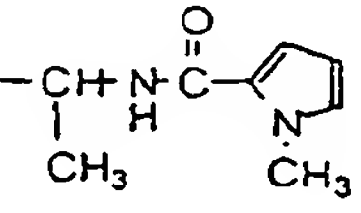
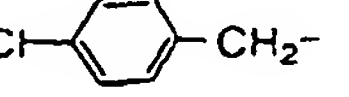
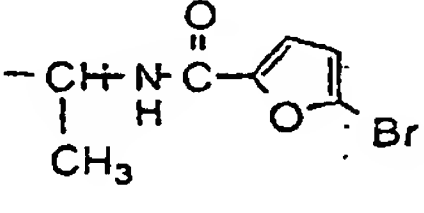
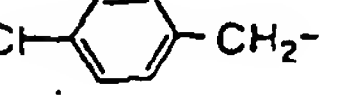
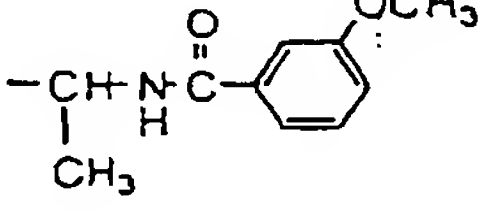
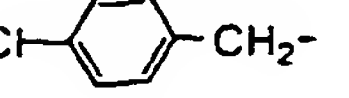
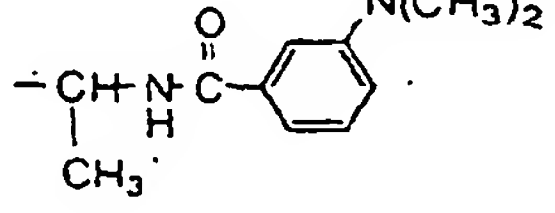
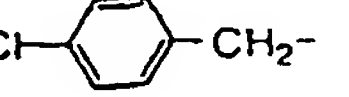
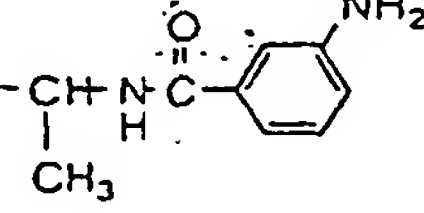
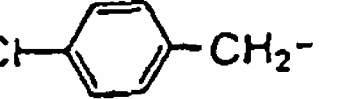
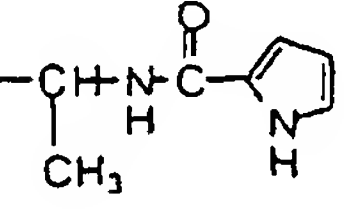
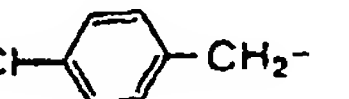
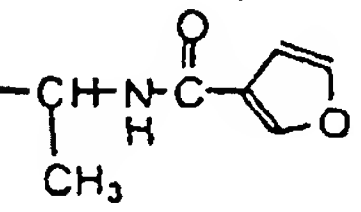
5 10 15 20 25 30 35 40 45 50 55	Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_l -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
	595		2	2	1	-	H	
	596		2	2	1	-	H	
	597		2	2	1	-	H	
	598		2	2	1	-	H	
	599		2	2	1	-	H	
	600		2	2	1	-	H	
	601		2	2	1	-	H	
	602		2	2	1	-	H	
	603		2	2	1	-	H	
	604		2	2	1	-	H	
	605		2	2	1	-	H	

Table 1.56

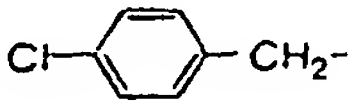
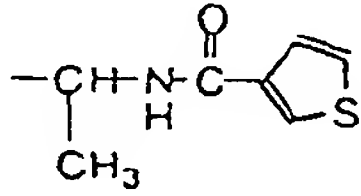
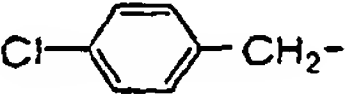
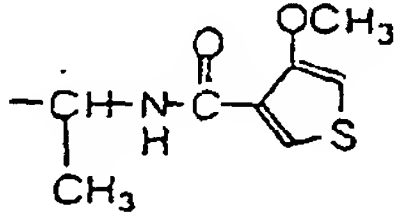
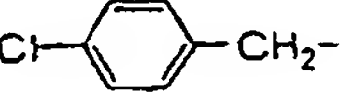
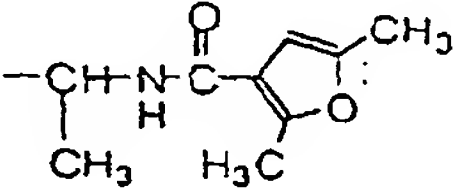
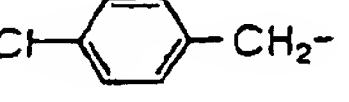
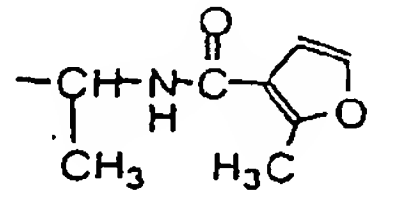
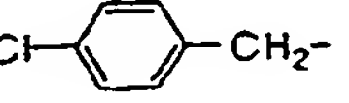
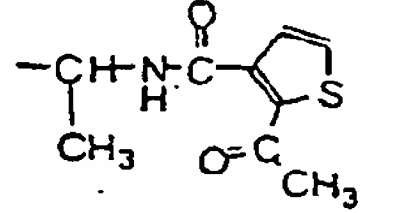

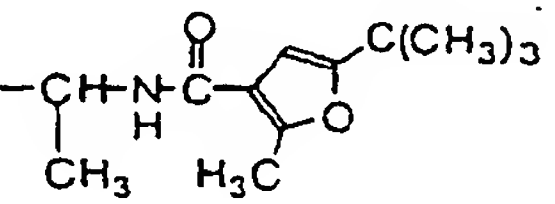
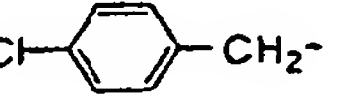
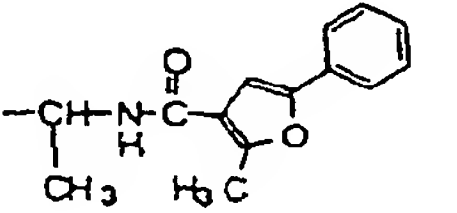
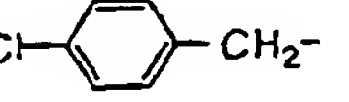
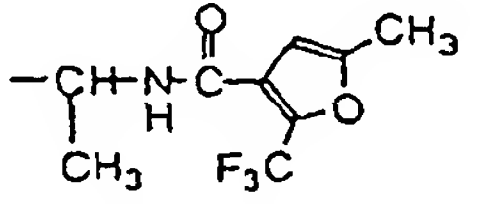
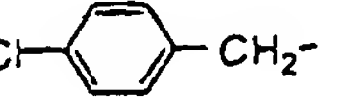
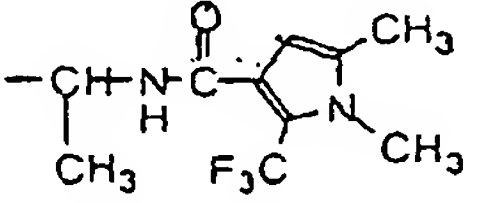
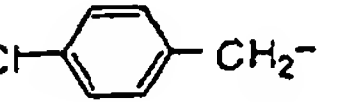
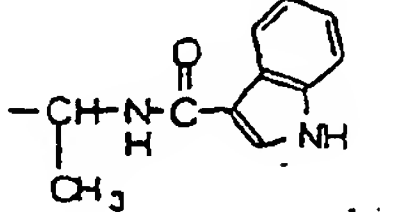
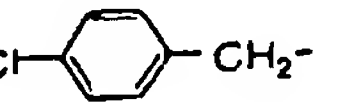
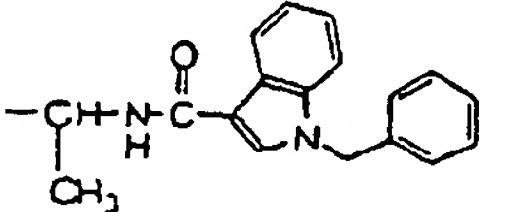
5	Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
10	606		2	2	1	-	H	
15	607		2	2	1	-	H	
20	608		2	2	1	-	H	
25	609		2	2	1	-	H	
30	610		2	2	1	-	H	
35	611		2	2	1	-	H	
40	612		2	2	1	-	H	
45	613		2	2	1	-	H	
50	614		2	2	1	-	H	
55	615		2	2	1	-	H	
	616		2	2	1	-	H	

Table 1.5 7

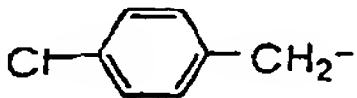
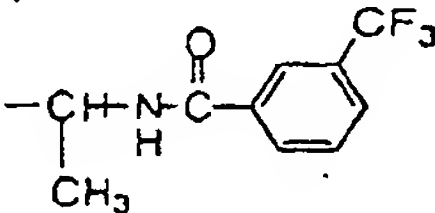
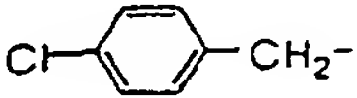
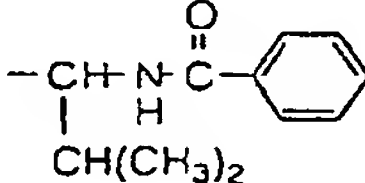
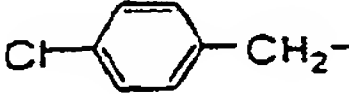
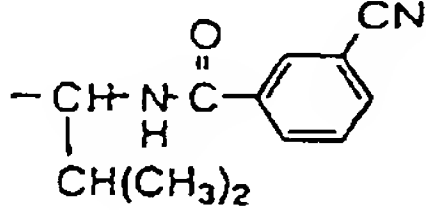
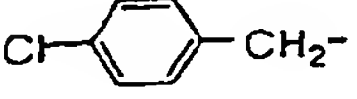
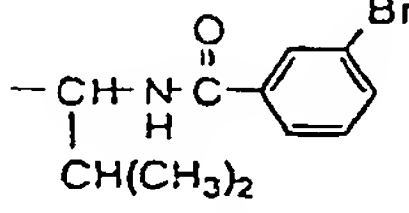
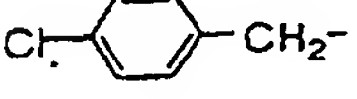
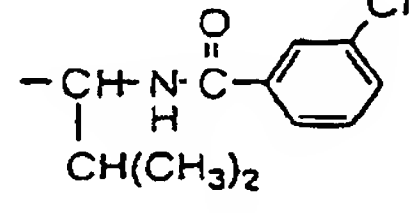
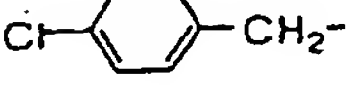
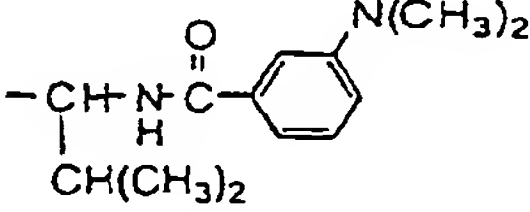
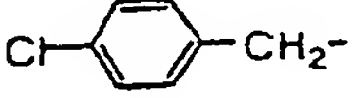
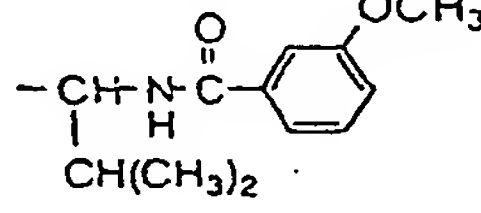
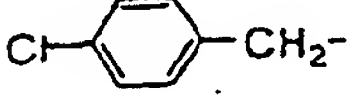
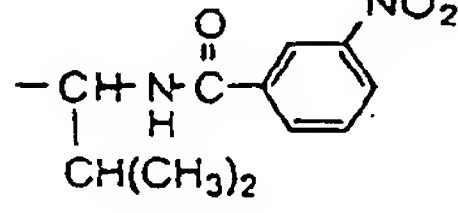
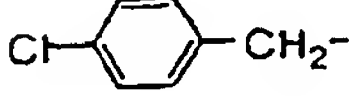
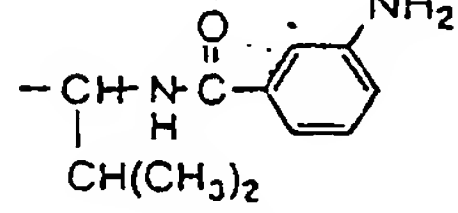
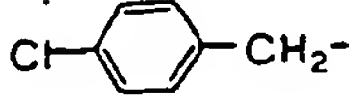
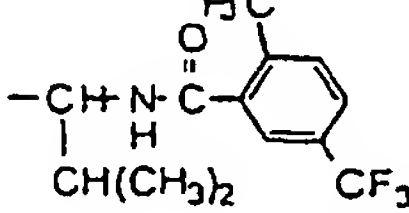
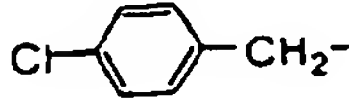
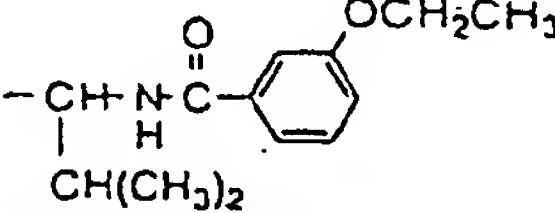
5	Compd. No.	$\begin{array}{c} R^1 \\ \\ R^2 \end{array} \text{---} (\text{CH}_2)_j \text{---}$	k	m	n	chirality	R^3	$-(\text{CH}_2)_p \text{---} \begin{array}{c} R^4 \\ \\ R^5 \end{array} \text{---} (\text{CH}_2)_q \text{---} \text{G---} R^6$
10	617		2	2	1	-	H	
15	618		2	2	1	-	H	
20	619		2	2	1	-	H	
25	620		2	2	1	-	H	
30	621		2	2	1	-	H	
35	622		2	2	1	-	H	
40	623		2	2	1	-	H	
45	624		2	2	1	-	H	
50	625		2	2	1	-	H	
55	626		2	2	1	-	H	
	627		2	2	1	-	H	

Table 1.5 8


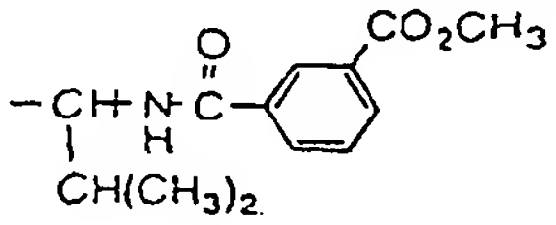
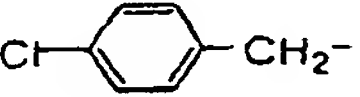
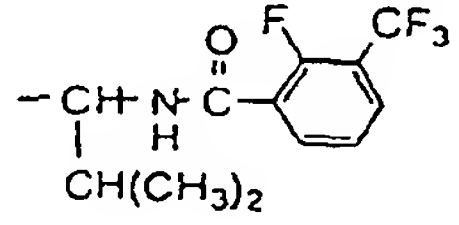
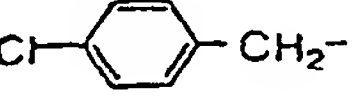
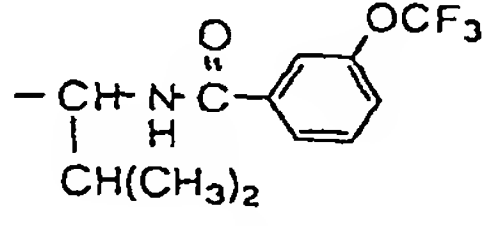
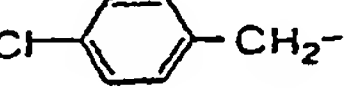
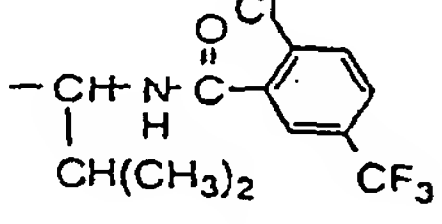

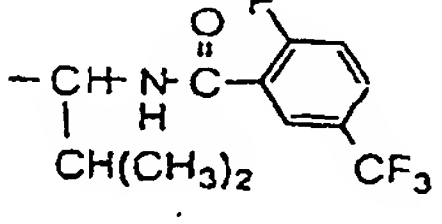
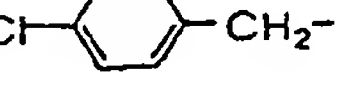
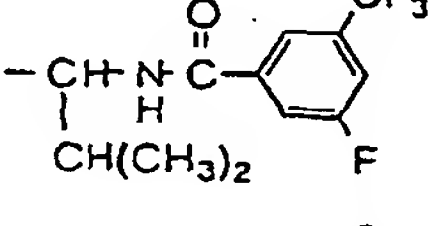
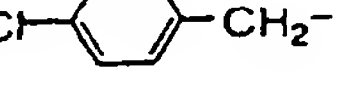
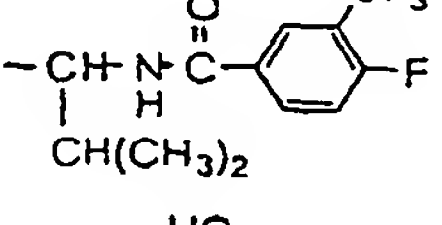
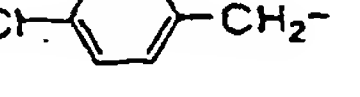
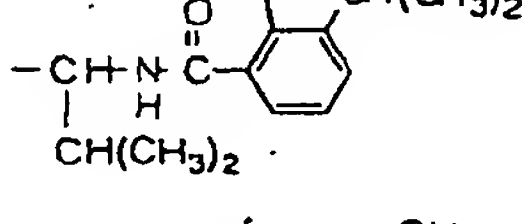
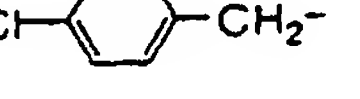
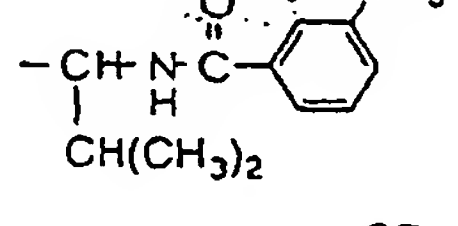
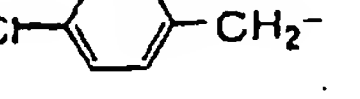
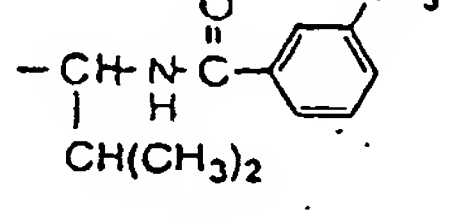
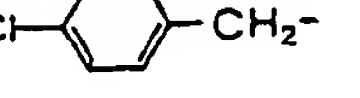
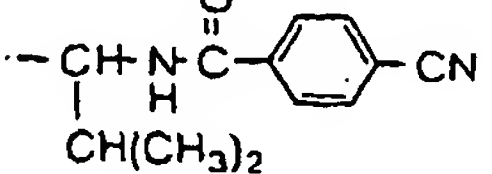
Compd. No.	$\begin{array}{c} R^1 \\ \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
628		2	2	1	-	H	
629		2	2	1	-	H	
630		2	2	1	-	H	
631		2	2	1	-	H	
632		2	2	1	-	H	
633		2	2	1	-	H	
634		2	2	1	-	H	
635		2	2	1	-	H	
636		2	2	1	-	H	
637		2	2	1	-	H	
638		2	2	1	-	H	

Table 1.59

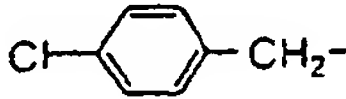
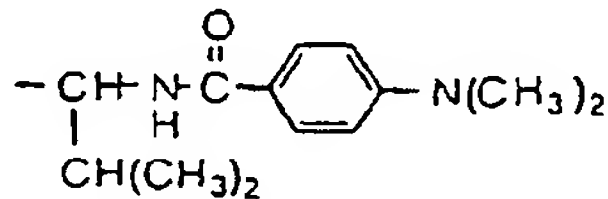

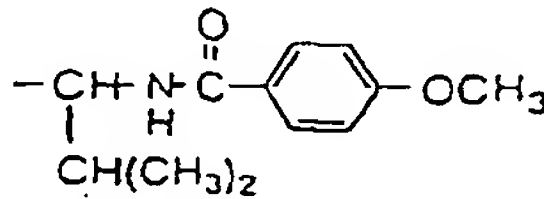
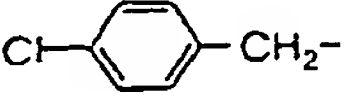
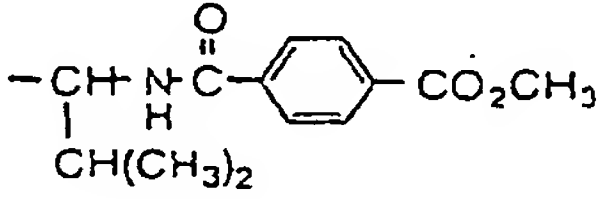
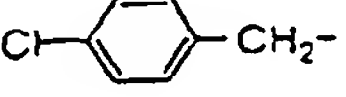
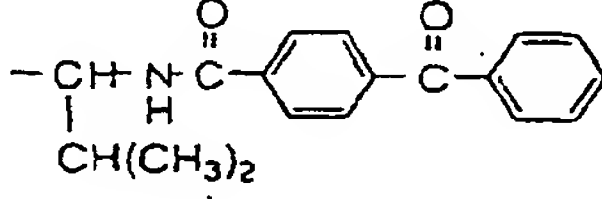
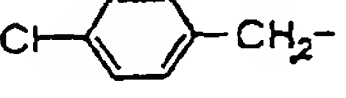
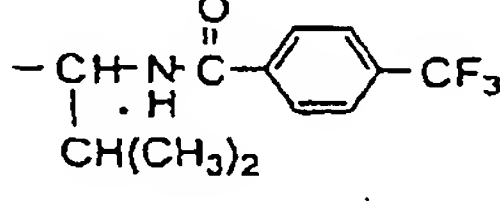
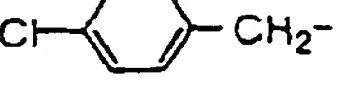
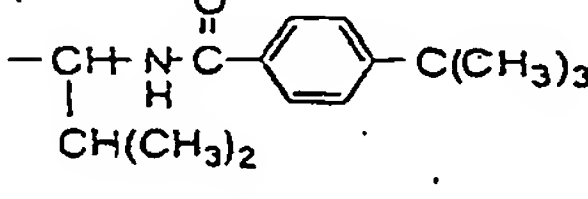
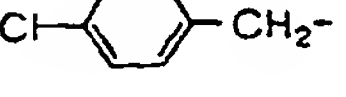
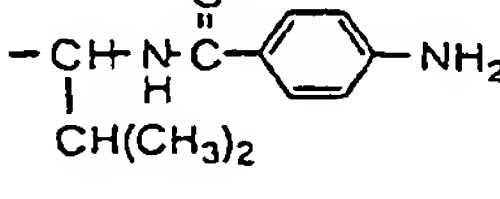
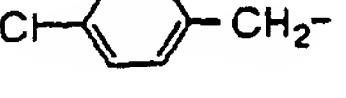
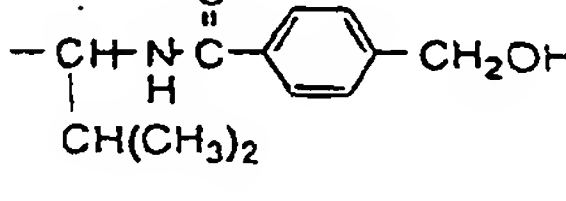
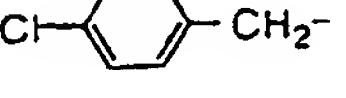
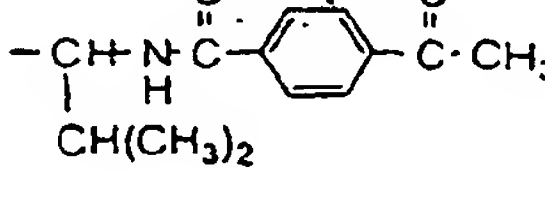
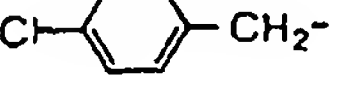
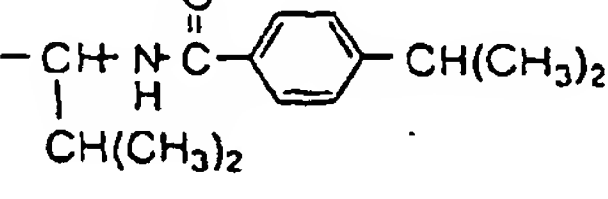
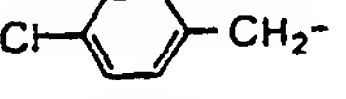
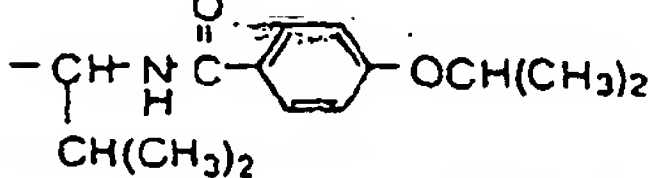
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_k- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p-\overset{\overset{R^4}{ }}{\underset{\underset{R^5}{ }}{C}}-(CH_2)_q-G-R^6$
639		2	2	1	-	H	
640		2	2	1	-	H	
641		2	2	1	-	H	
642		2	2	1	-	H	
643		2	2	1	-	H	
644		2	2	1	-	H	
645		2	2	1	-	H	
646		2	2	1	-	H	
647		2	2	1	-	H	
648		2	2	1	-	H	
649		2	2	1	-	H	

Table 1.6 0

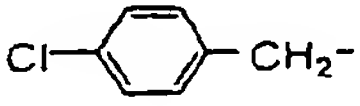
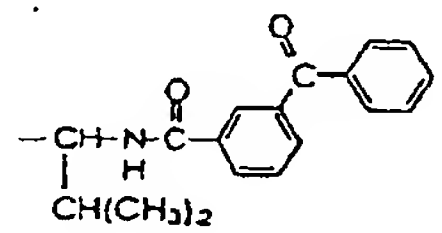
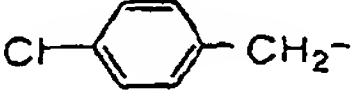
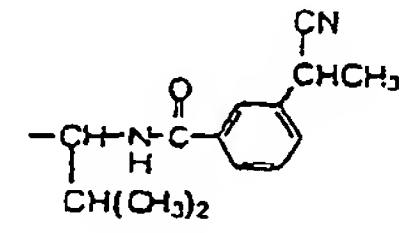
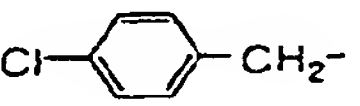
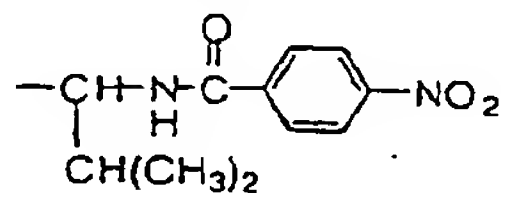
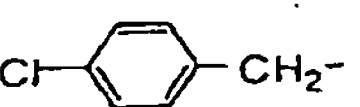
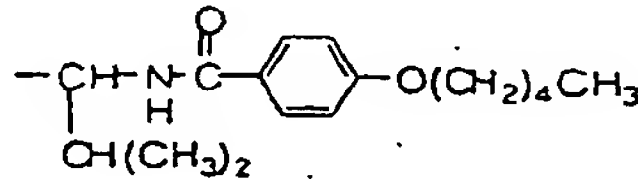
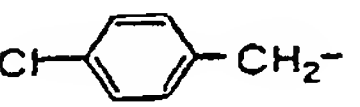
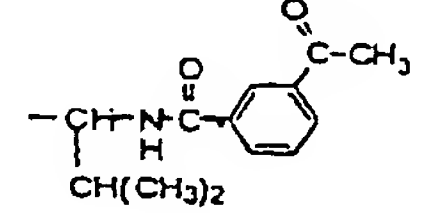

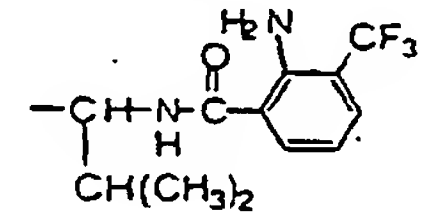
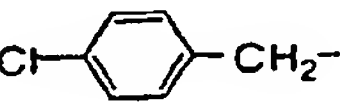
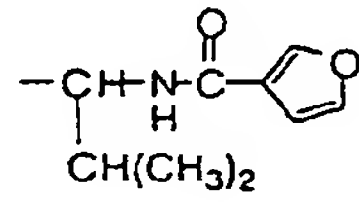
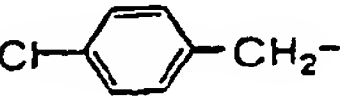
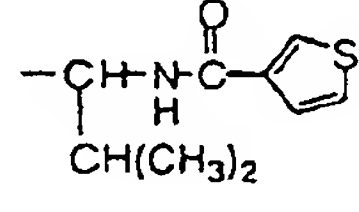
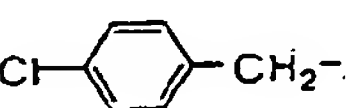
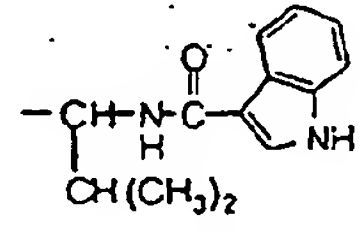
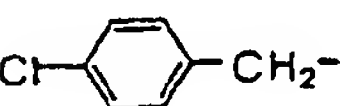
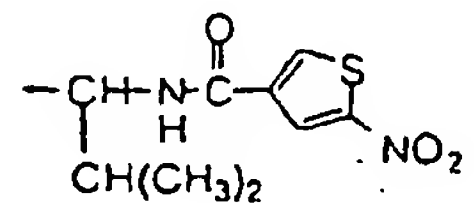
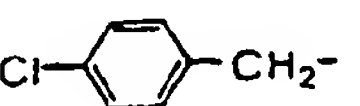
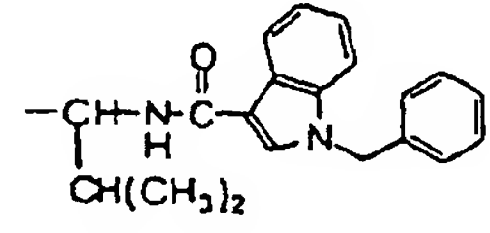
5	Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ R^2 \end{matrix} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
10	650		2	2	1	-	H	
15	651		2	2	1	-	H	
20	652		2	2	1	-	H	
25	653		2	2	1	-	H	
30	654		2	2	1	-	H	
35	655		2	2	1	-	H	
40	656		2	2	1	-	H	
45	657		2	2	1	-	H	
50	658		2	2	1	-	H	
	659		2	2	1	-	H	
	660		2	2	1	-	H	

Table 1.6 1

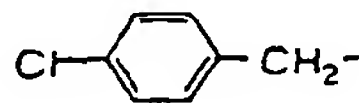
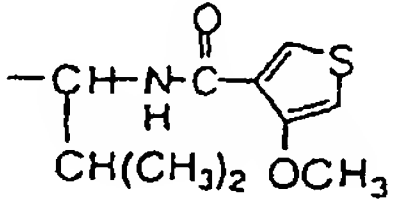
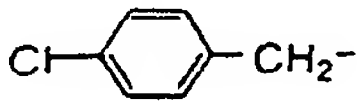
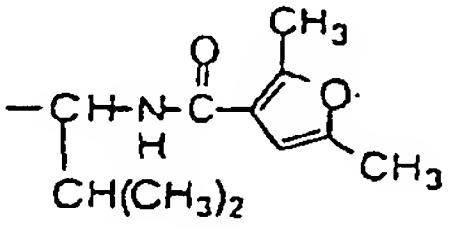
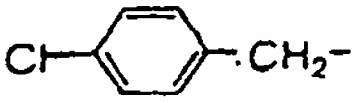
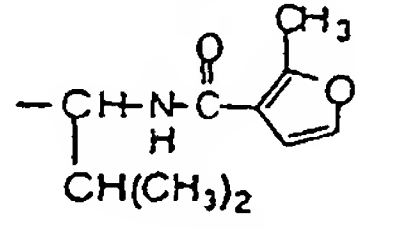
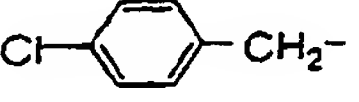
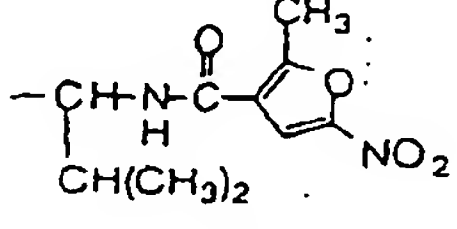
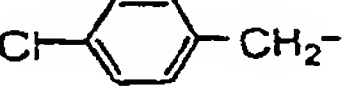
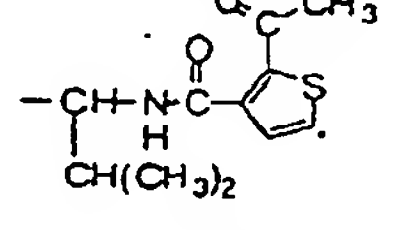
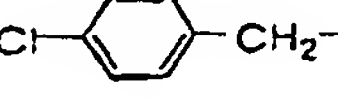
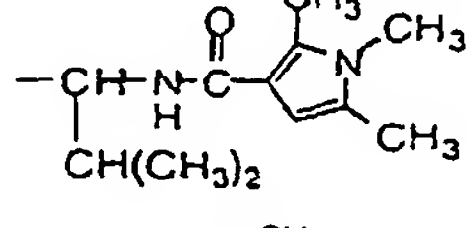
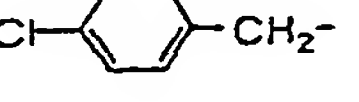
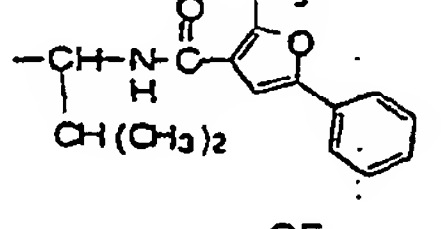
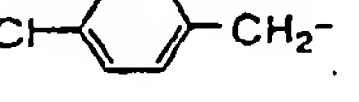
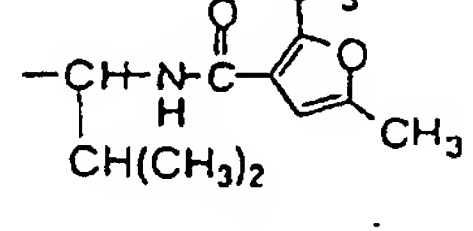
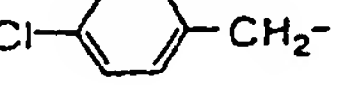
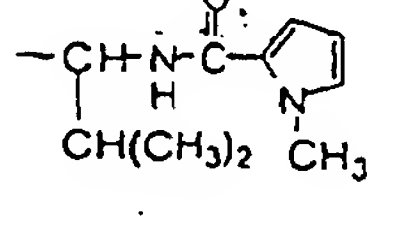
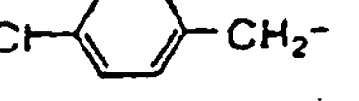
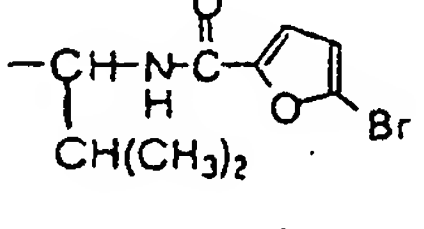
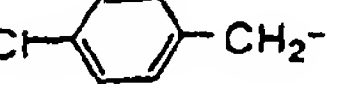
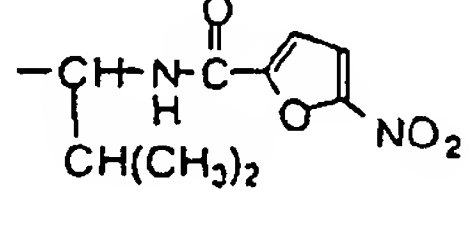
5	Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_l- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
10	661		2	2	1	-	H	
15	662		2	2	1	-	H	
20	663		2	2	1	-	H	
25	664		2	2	1	-	H	
30	665		2	2	1	-	H	
35	666		2	2	1	-	H	
40	667		2	2	1	-	H	
45	668		2	2	1	-	H	
50	669		2	2	1	-	H	
55	670		2	2	1	-	H	
	671		2	2	1	-	H	

Table 1.62

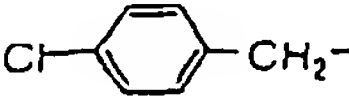
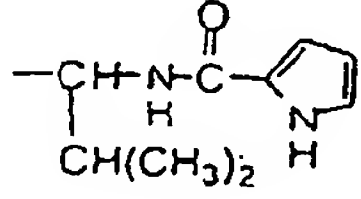
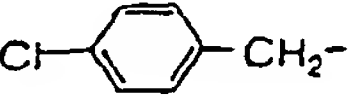
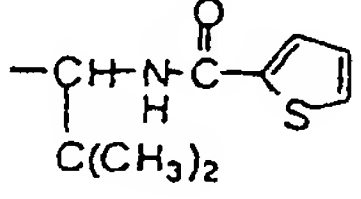
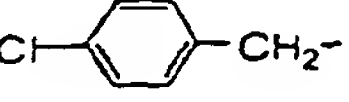
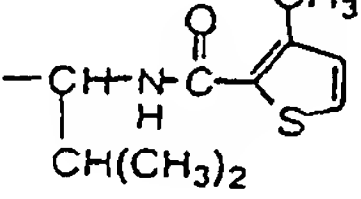
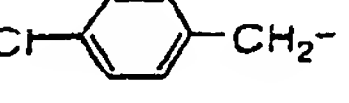
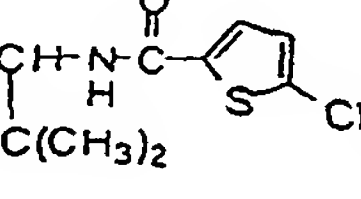
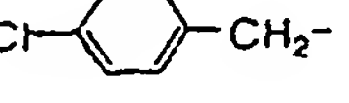
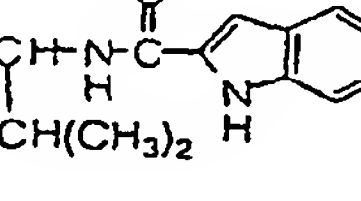

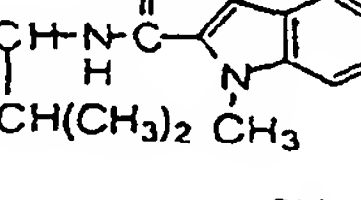
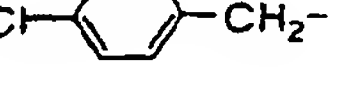
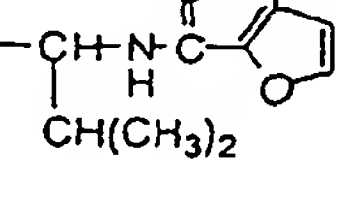
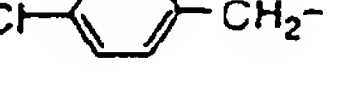
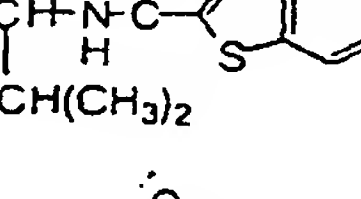
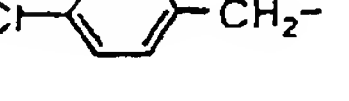
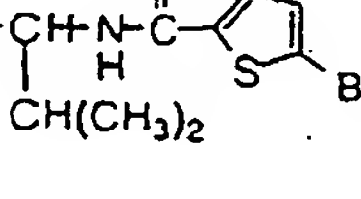
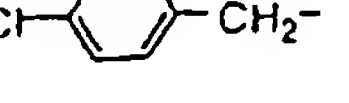
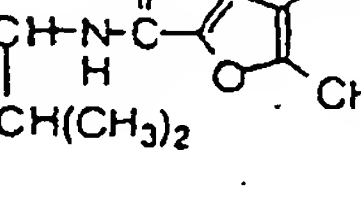
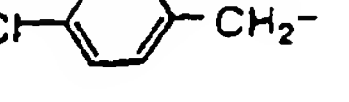
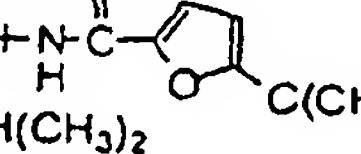
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_i$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
672		2	2	1	-	H	
673		2	2	1	-	H	
674		2	2	1	-	H	
675		2	2	1	-	H	
676		2	2	1	-	H	
677		2	2	1	-	H	
678		2	2	1	-	H	
679		2	2	1	-	H	
680		2	2	1	-	H	
681		2	2	1	-	H	
682		2	2	1	-	H	

Table 1.63

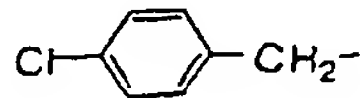
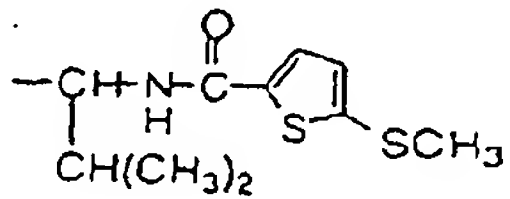
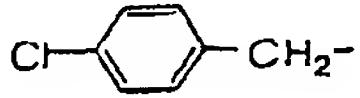
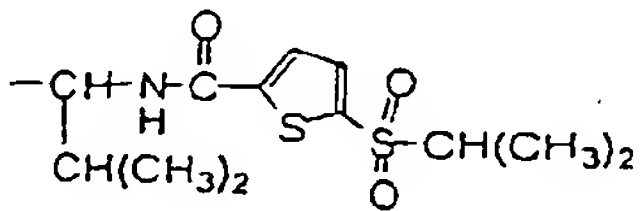
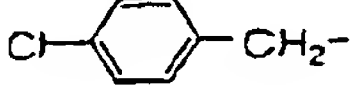
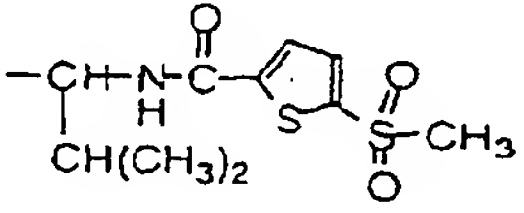
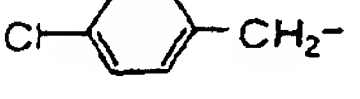
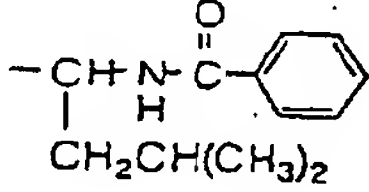
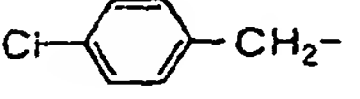
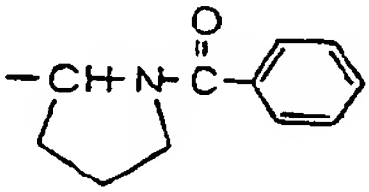
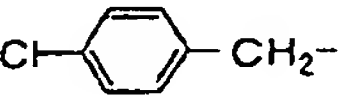
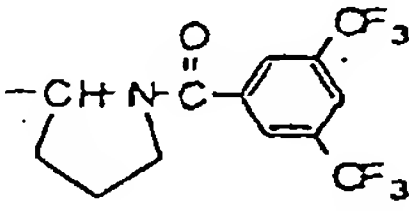
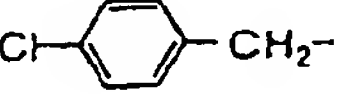
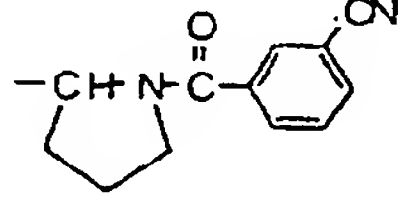
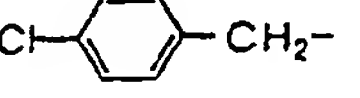
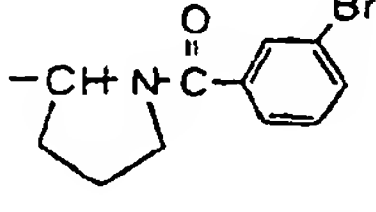
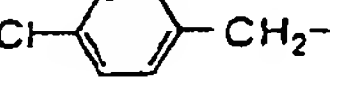
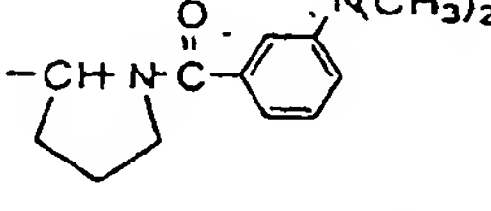
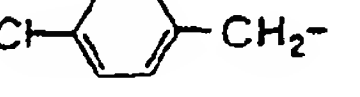
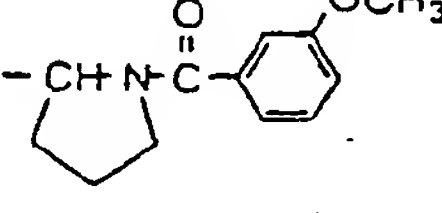
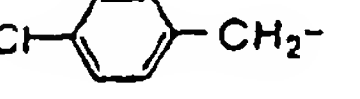
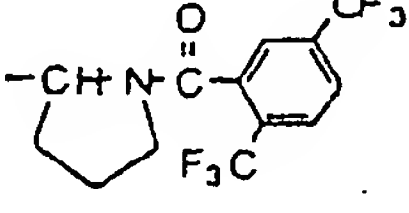
Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (\text{CH}_2)_j \text{---}$	k	m	n	chirality	R^3	$-(\text{CH}_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} \text{---} (\text{CH}_2)_q \text{---} \text{G---} R^6$
683		2	2	1	-	H	
684		2	2	1	-	H	
685		2	2	1	-	H	
686		2	2	1	-	H	
687		2	2	1	-	H	
688		2	2	1	-	H	
689		2	2	1	-	H	
690		2	2	1	-	H	
691		2	2	1	-	H	
692		2	2	1	-	H	
693		2	2	1	-	H	

Table 1.6 4


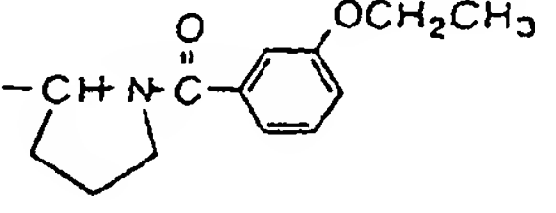

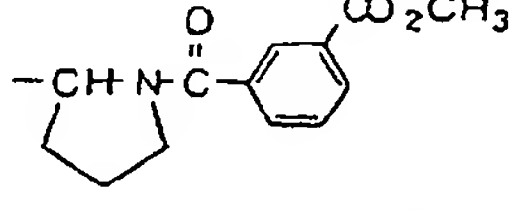

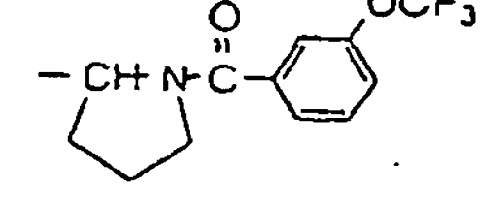
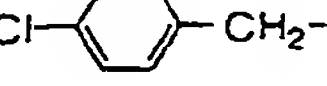
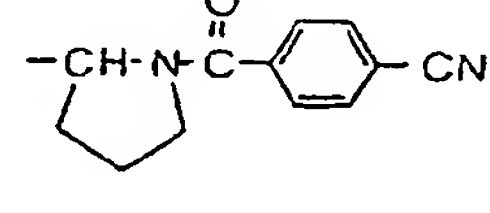
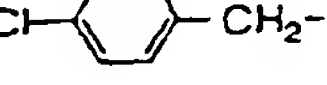
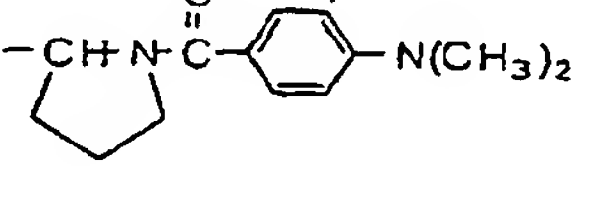
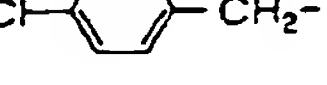
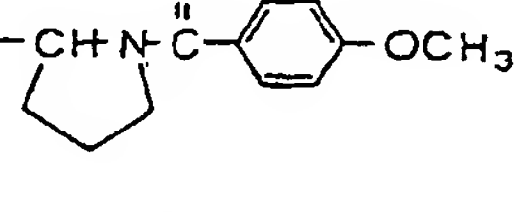

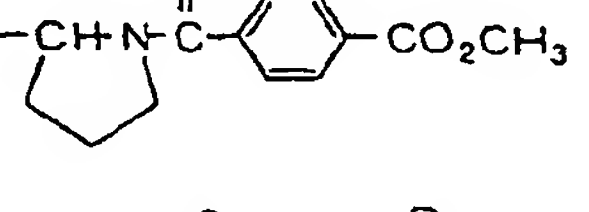

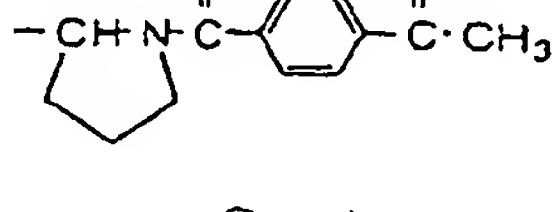

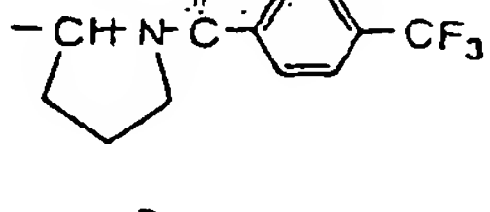

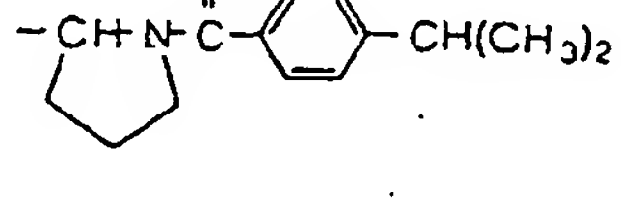
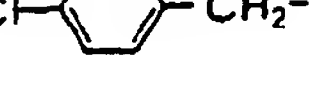
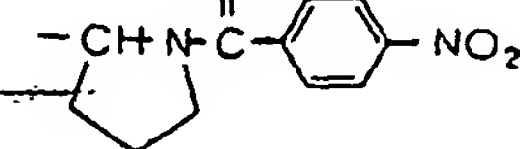
Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ R^2 \end{matrix} (CH_2)_i -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
694		2	2	1	-	H	
695		2	2	1	-	H	
696		2	2	1	-	H	
697		2	2	1	-	H	
698		2	2	1	-	H	
699		2	2	1	-	H	
700		2	2	1	-	H	
701		2	2	1	-	H	
702		2	2	1	-	H	
703		2	2	1	-	H	
704		2	2	1	-	H	

Table 1.6 5

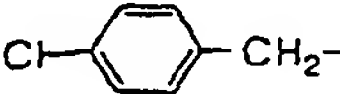
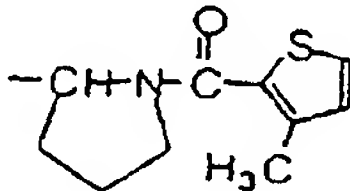
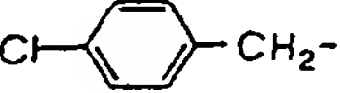
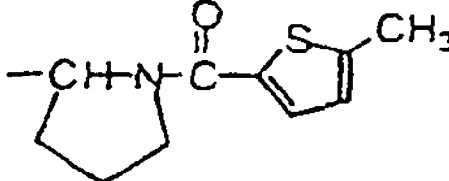
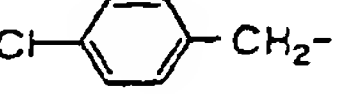
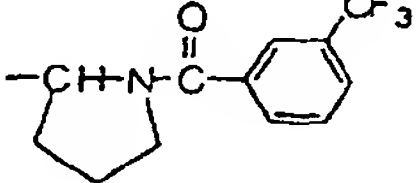

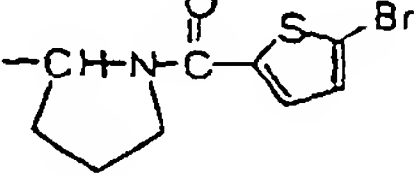

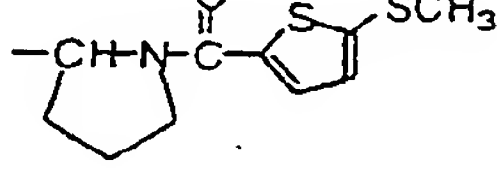
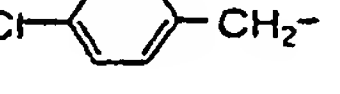
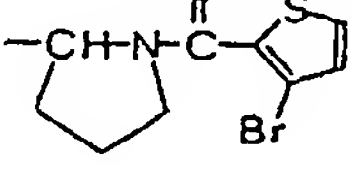
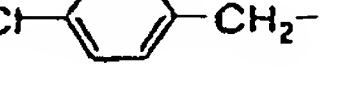
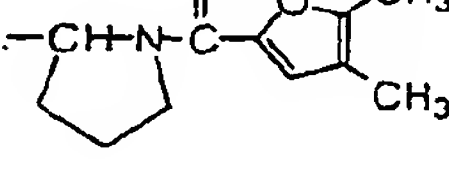
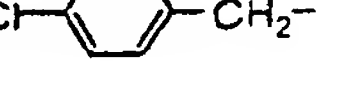
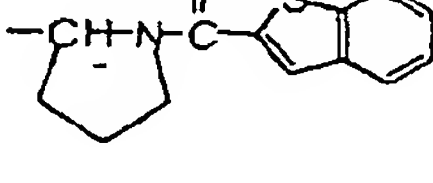
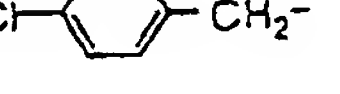
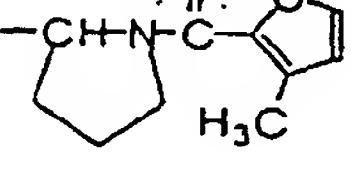
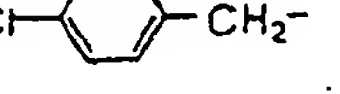
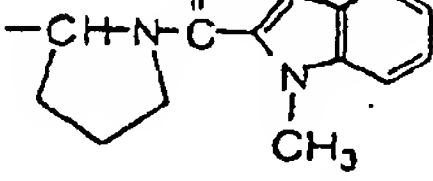
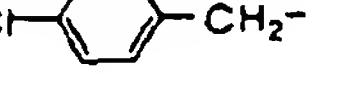
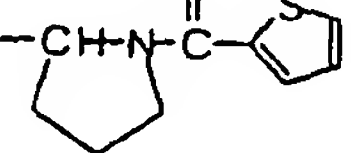
Compd. No.	$\begin{array}{c} R^1 \\ \\ R^2 \end{array} \text{---} (CH_2)_l \text{---}$	k	m	n	chirality	R^3	$-(CH_2)_p \text{---} \begin{array}{c} R^4 \\ \\ R^5 \end{array} \text{---} (CH_2)_q \text{---} G \text{---} R^6$
705		2	2	1	-	H	
706		2	2	1	-	H	
707		2	2	1	-	H	
708		2	2	1	-	H	
709		2	2	1	-	H	
710		2	2	1	-	H	
711		2	2	1	-	H	
712		2	2	1	-	H	
713		2	2	1	-	H	
714		2	2	1	-	H	
715		2	2	1	-	H	

Table 1.6 6

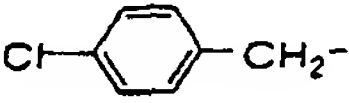
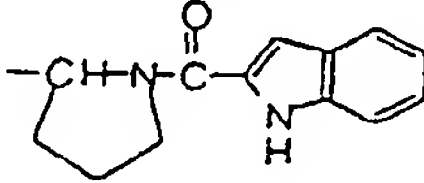
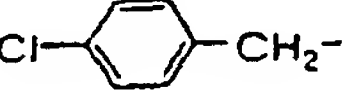
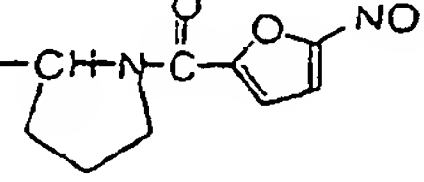
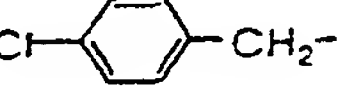
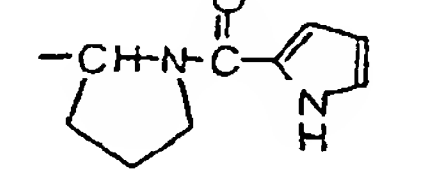
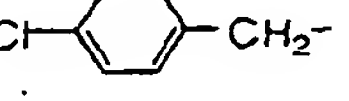
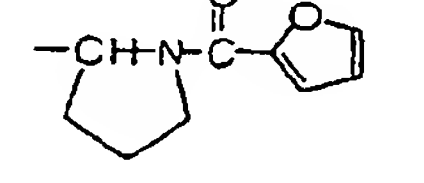
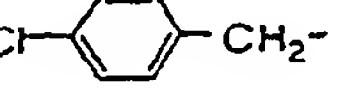
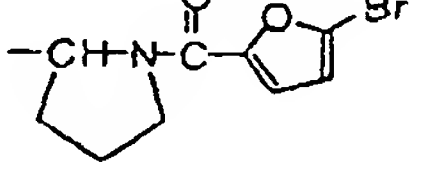
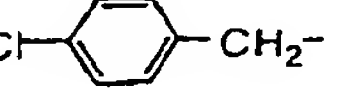
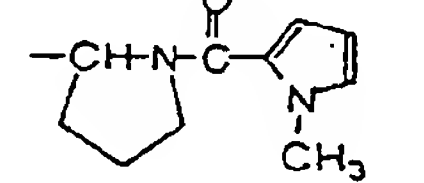
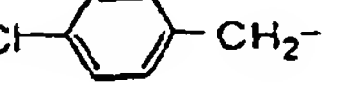
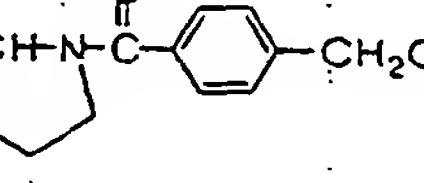
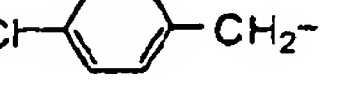
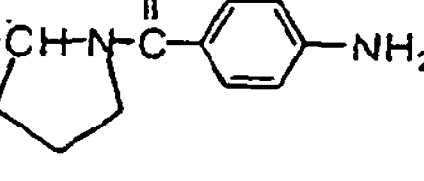
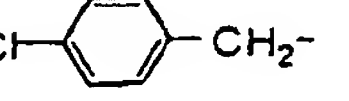
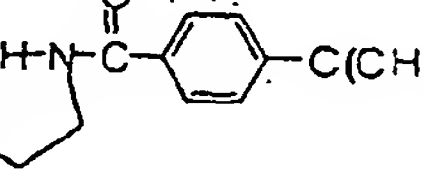
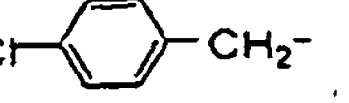
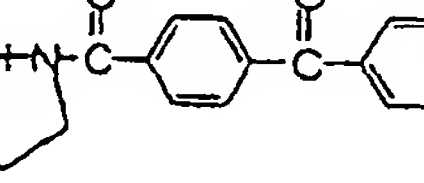
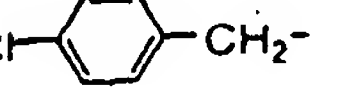
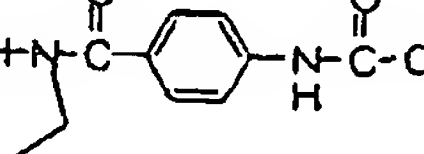
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_l- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ -C- \\ \\ R^5 \end{array} (CH_2)_q -G-R^6$
716		2	2	1	-	H	
717		2	2	1	-	H	
718		2	2	1	-	H	
719		2	2	1	-	H	
720		2	2	1	-	H	
721		2	2	1	-	H	
722		2	2	1	-	H	
723		2	2	1	-	H	
724		2	2	1	-	H	
725		2	2	1	-	H	
726		2	2	1	-	H	

Table 1.67

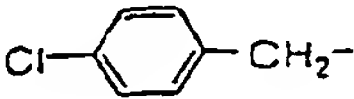
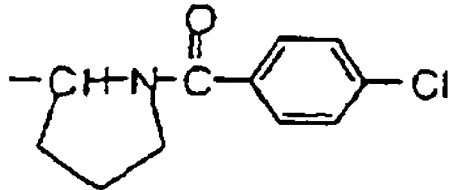
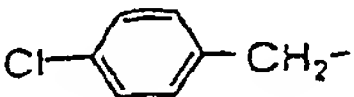
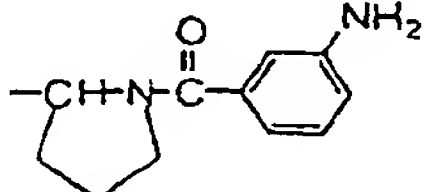
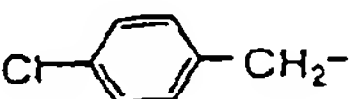
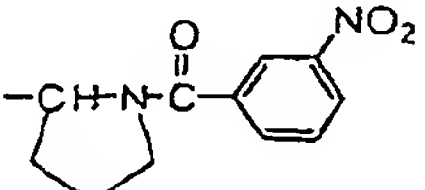
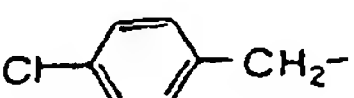
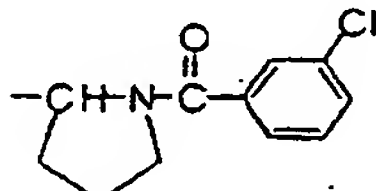
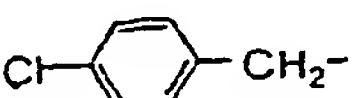
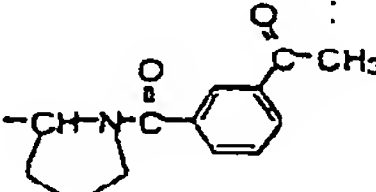

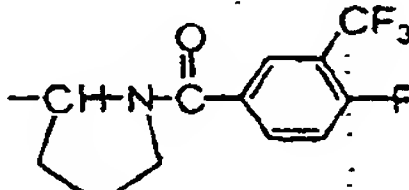

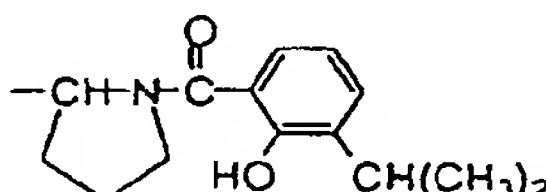
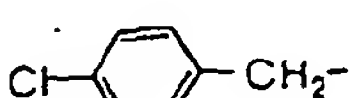
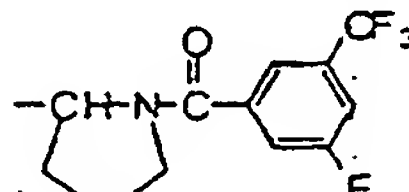
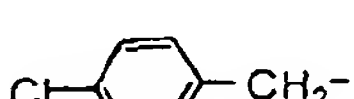
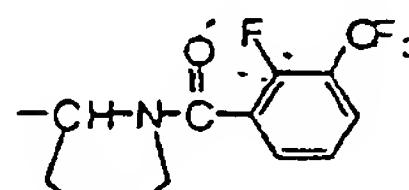

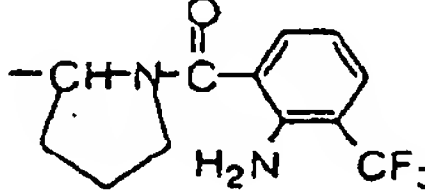

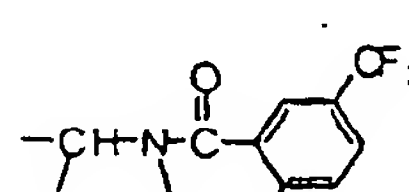
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ (CH_2)_q \\ \\ R^5 \end{array} G-R^6$
727		2	2	1	-	H	
728		2	2	1	-	H	
729		2	2	1	-	H	
730		2	2	1	-	H	
731		2	2	1	-	H	
732		2	2	1	-	H	
733		2	2	1	-	H	
734		2	2	1	-	H	
735		2	2	1	-	H	
736		2	2	1	-	H	
737		2	2	1	-	H	

Table 1.68

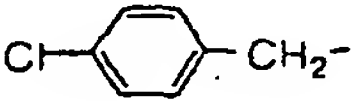
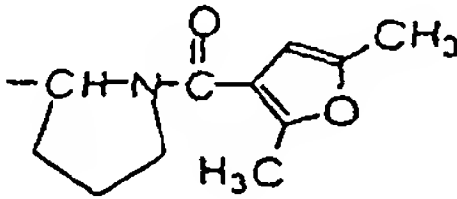
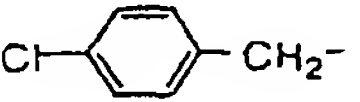
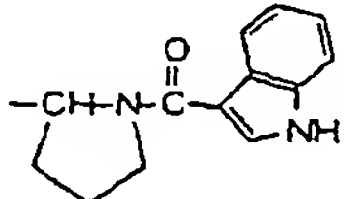
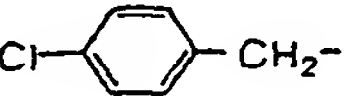
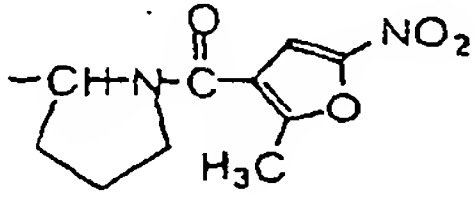
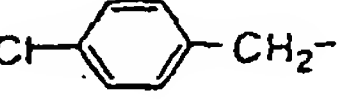
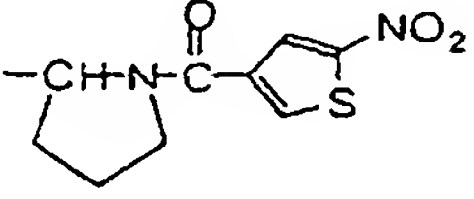
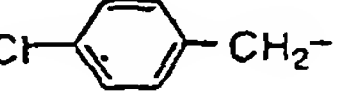
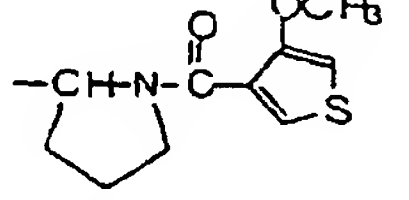
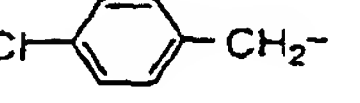
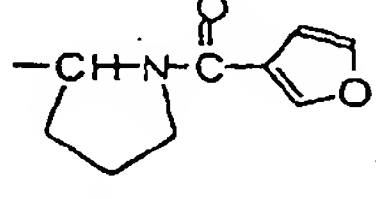
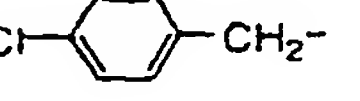
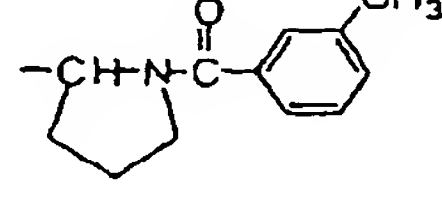
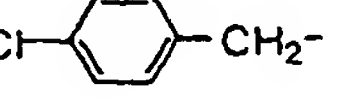
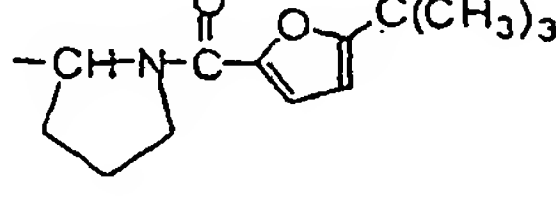
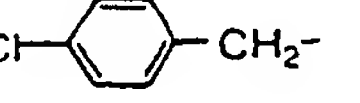
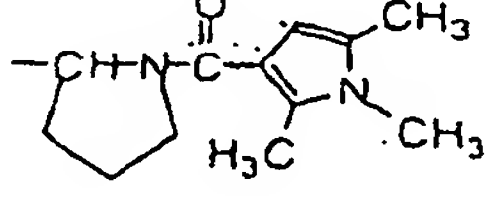
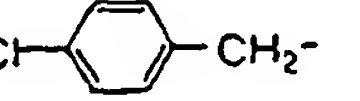
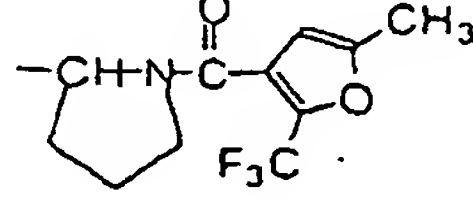
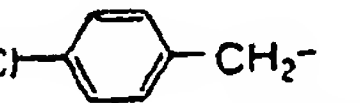
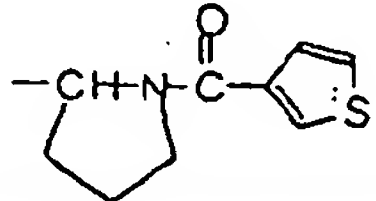
5	Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
10	738		2	2	1	-	H	
15	739		2	2	1	-	H	
20	740		2	2	1	-	H	
25	741		2	2	1	-	H	
30	742		2	2	1	-	H	
35	743		2	2	1	-	H	
40	744		2	2	1	-	H	
45	745		2	2	1	-	H	
50	746		2	2	1	-	H	
55	747		2	2	1	-	H	
	748		2	2	1	-	H	

Table 1.6 9

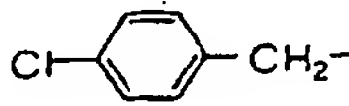
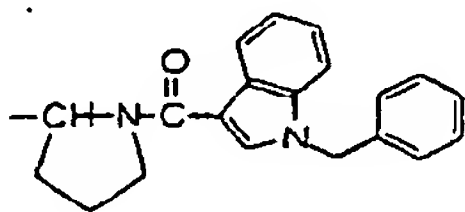
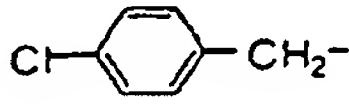
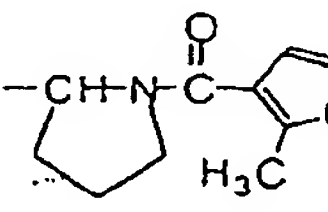
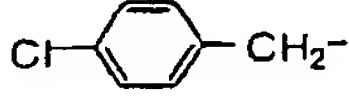
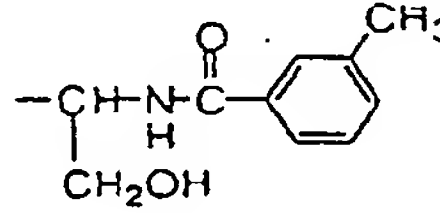
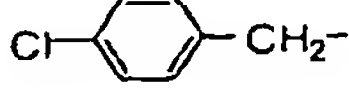
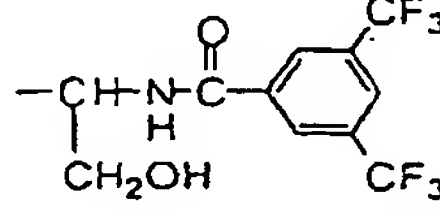
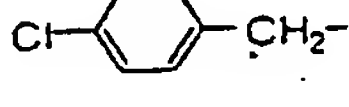
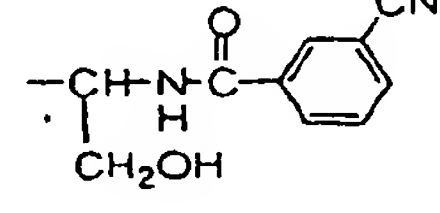
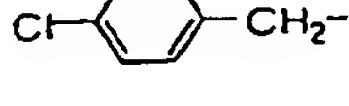
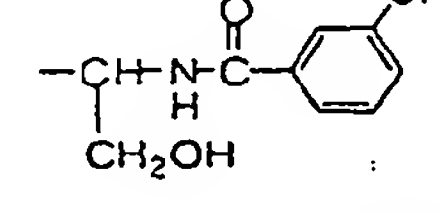
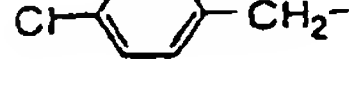
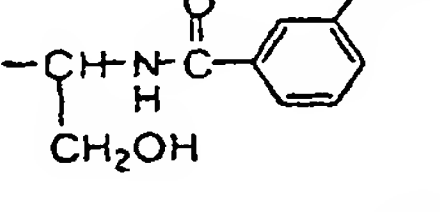
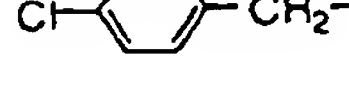
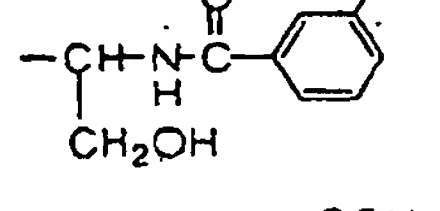
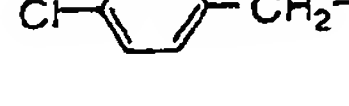
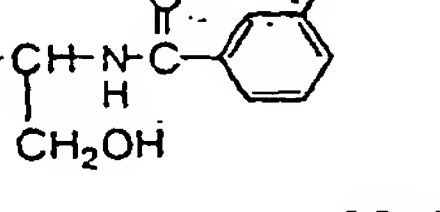
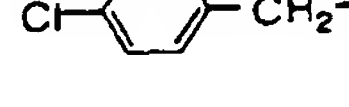
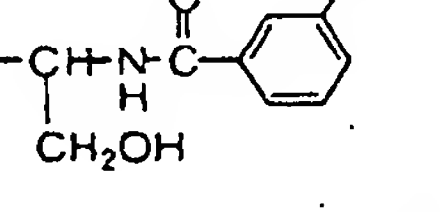
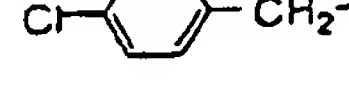
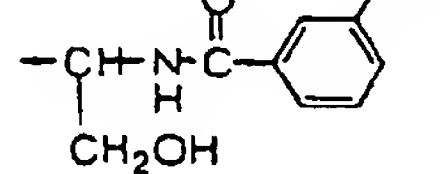
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_i \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
749		2	2	1	-	H	
750		2	2	1	-	H	
751		2	2	1	-	H	
752		2	2	1	-	H	
753		2	2	1	-	H	
754		2	2	1	-	H	
755		2	2	1	-	H	
756		2	2	1	-	H	
757		2	2	1	-	H	
758		2	2	1	-	H	
759		2	2	1	-	H	

Table 1.70

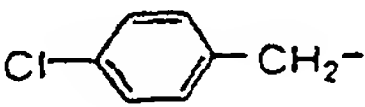
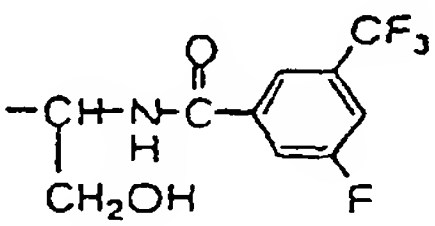

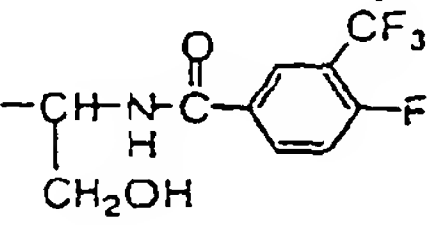
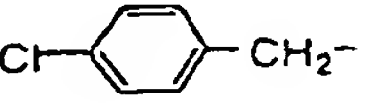
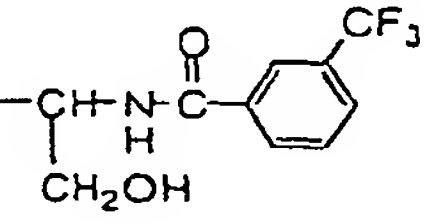

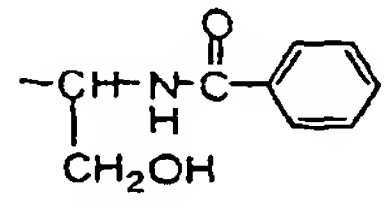

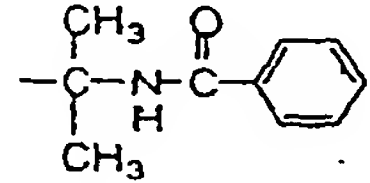
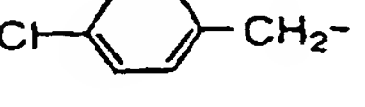
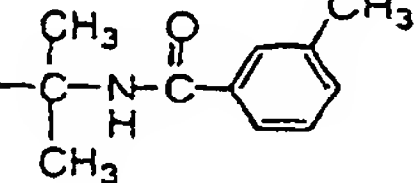
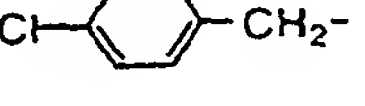
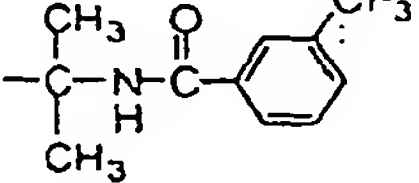
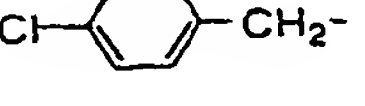
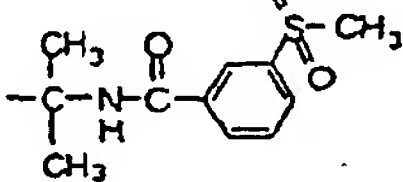
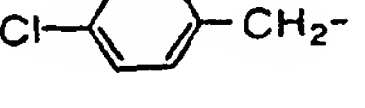
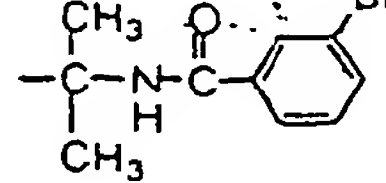
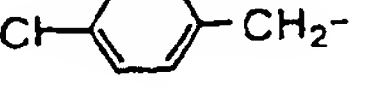
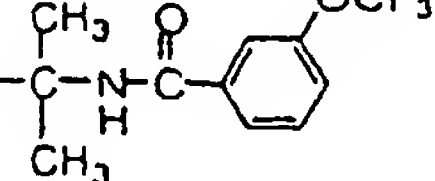

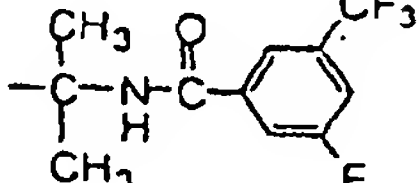
Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (CH_2)_l \text{---}$	k	m	n	chirality	R^3	$-(CH_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} \text{---} (CH_2)_q \text{---} G \text{---} R^6$
760		2	2	1	-	H	
761		2	2	1	-	H	
762		2	2	1	-	H	
763		2	2	1	-	H	
764		2	2	1	-	H	
765		2	2	1	-	H	
766		2	2	1	-	H	
767		2	2	1	-	H	
768		2	2	1	-	H	
769		2	2	1	-	H	
770		2	2	1	-	H	

Table 1.7 1

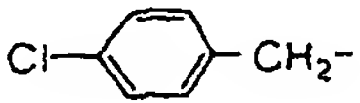
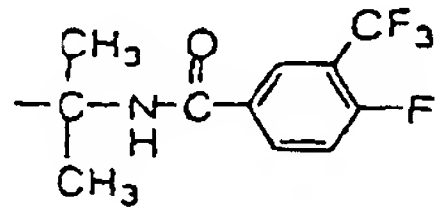
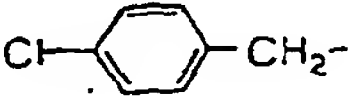
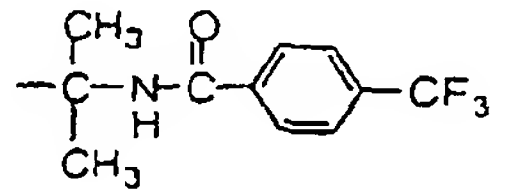
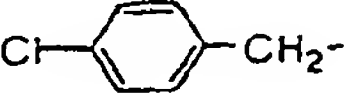
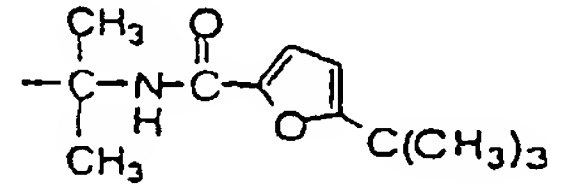
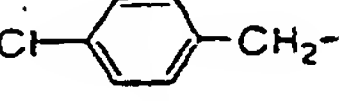
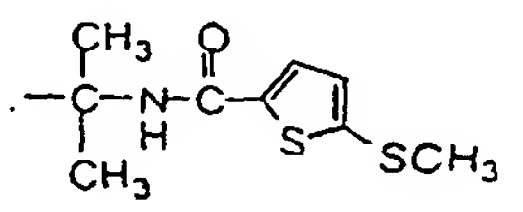

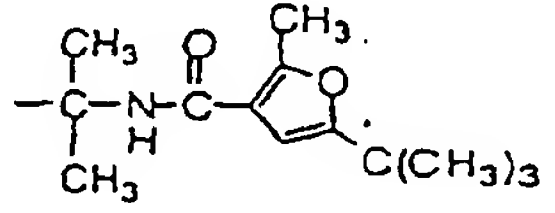

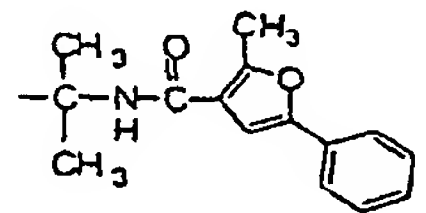
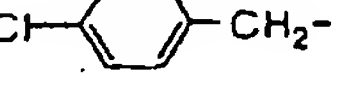
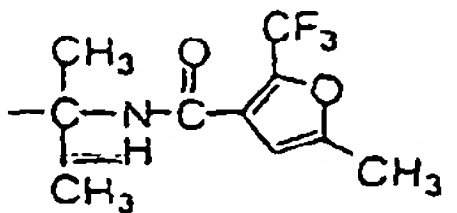
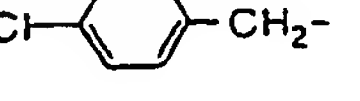
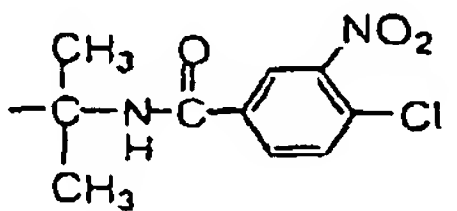
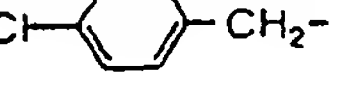
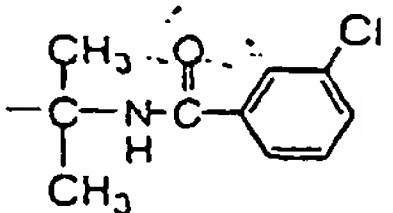
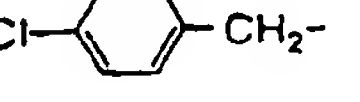
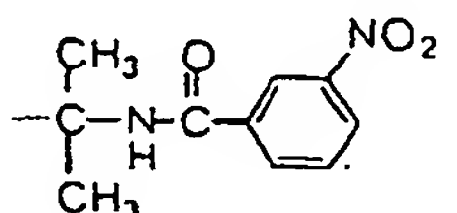
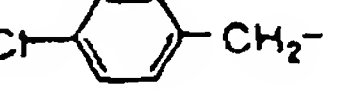
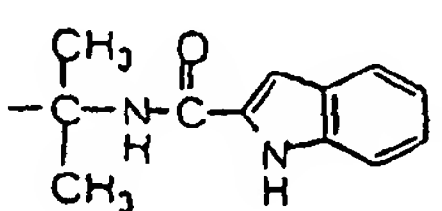
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_k \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ C \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
771		2	2	1	-	H	
772		2	2	1	-	H	
773		2	2	1	-	H	
774		2	2	1	-	H	
775		2	2	1	-	H	
776		2	2	1	-	H	
777		2	2	1	-	H	
778		2	2	1	-	H	
779		2	2	1	-	H	
780		2	2	1	-	H	
781		2	2	1	-	H	

Table 1.7 2

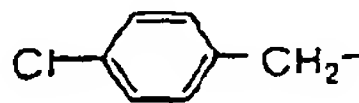
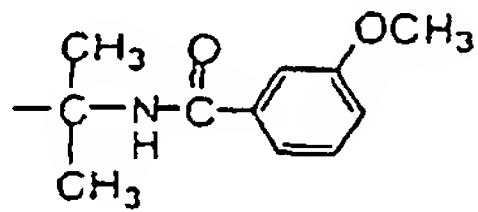
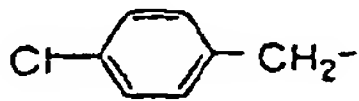
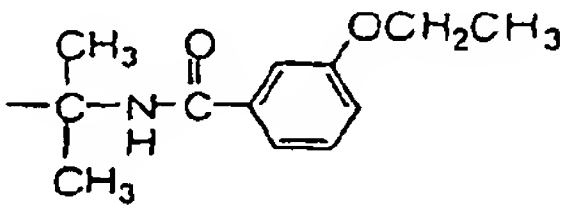
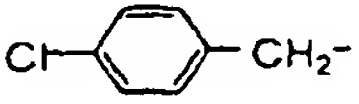
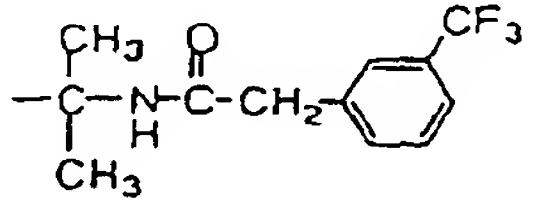
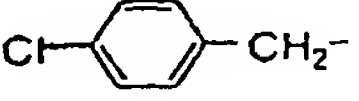
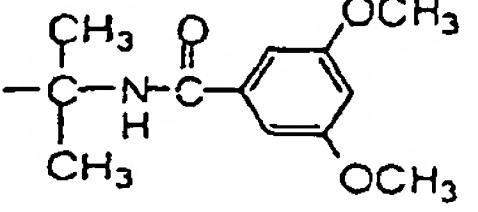
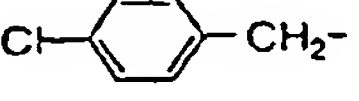
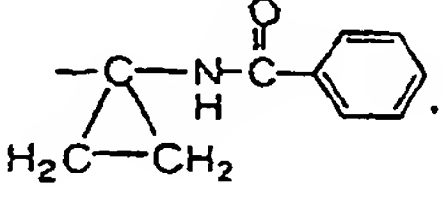

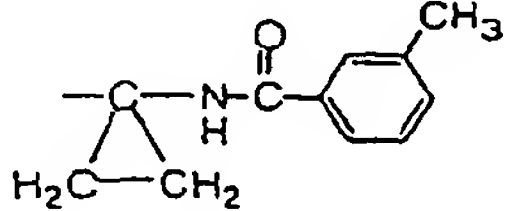
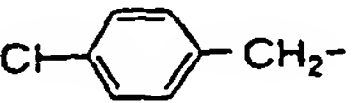
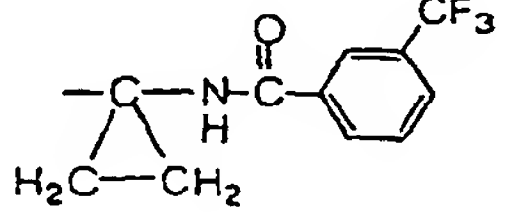
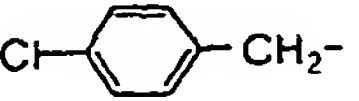
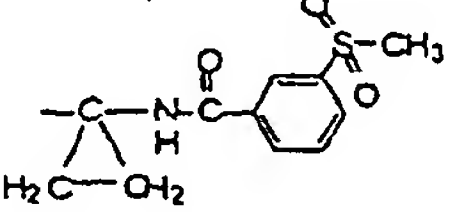
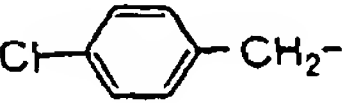
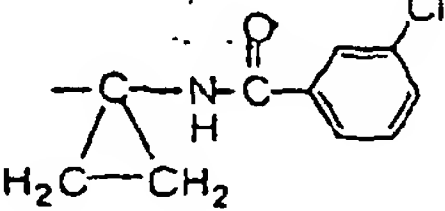
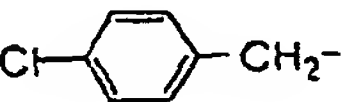
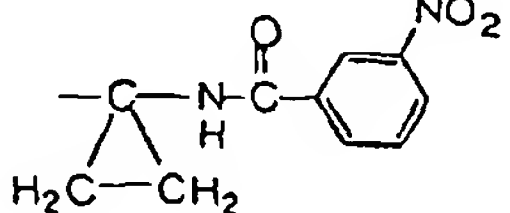
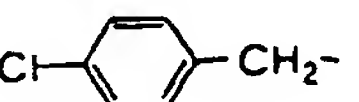
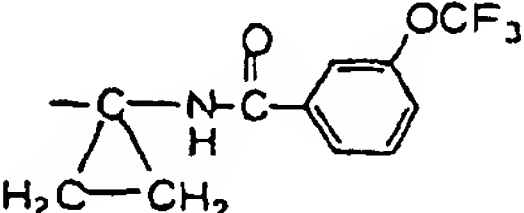
5	Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (\text{CH}_2)_j \text{---}$	k	m	n	chirality	R^3	$-(\text{CH}_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} \text{---} (\text{CH}_2)_q \text{---} G \text{---} R^6$
10	782		2	2	1	-	H	
15	783		2	2	1	-	H	
20	784		2	2	1	-	H	
25	785		2	2	1	-	H	
30	786		2	2	1	-	H	
35	787		2	2	1	-	H	
40	788		2	2	1	-	H	
45	789		2	2	1	-	H	
50	790		2	2	1	-	H	
55	791		2	2	1	-	H	
	792		2	2	1	-	H	

Table 1.7 3

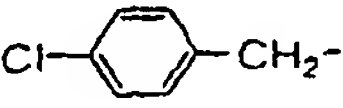
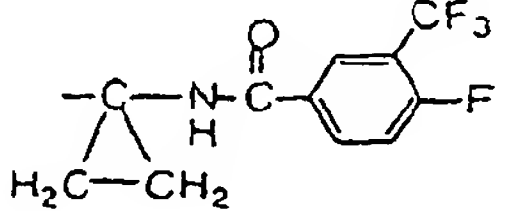
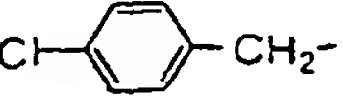
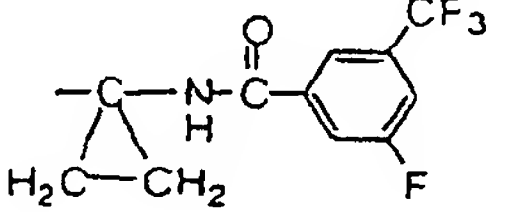
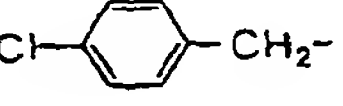
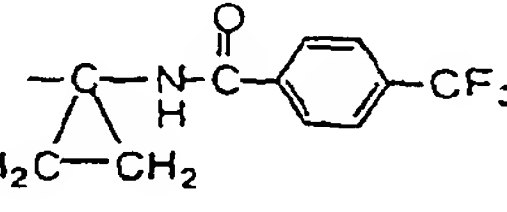
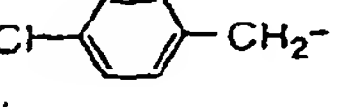
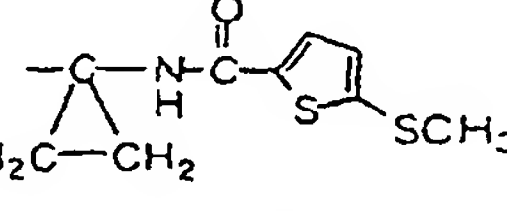
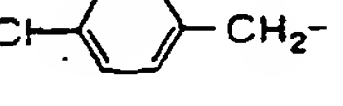
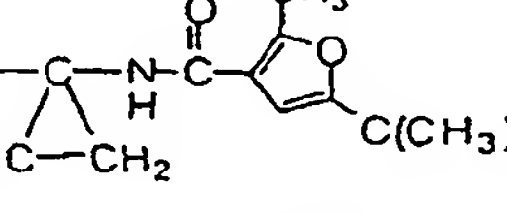

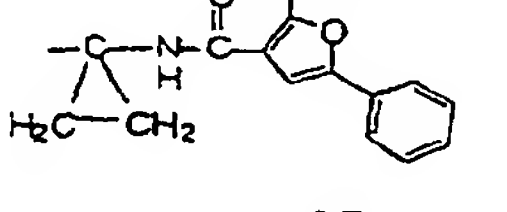
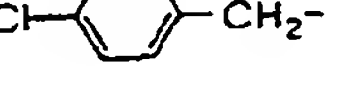
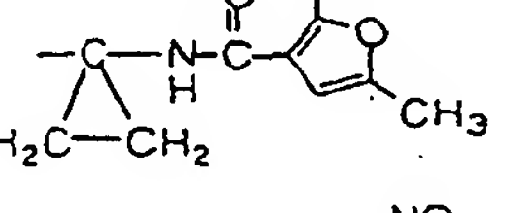
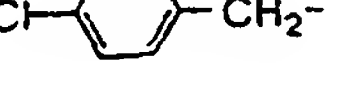
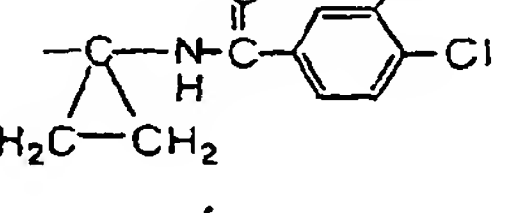
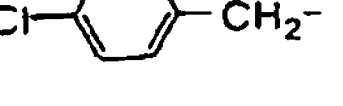
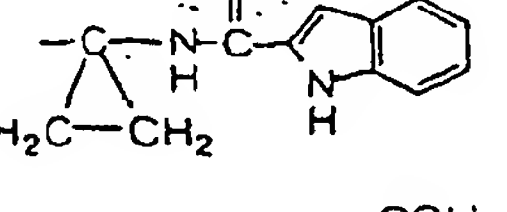
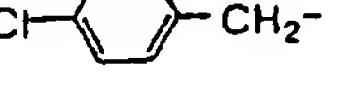
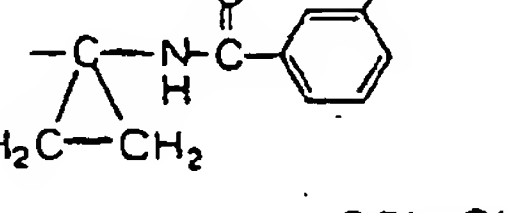
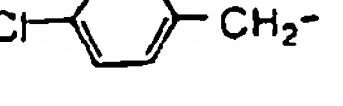
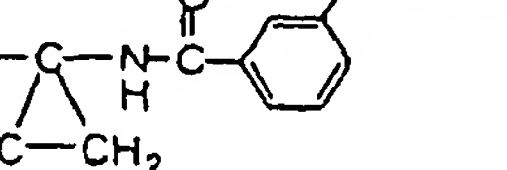
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
793		2	2	1	-	H	
794		2	2	1	-	H	
795		2	2	1	-	H	
796		2	2	1	-	H	
797		2	2	1	-	H	
798		2	2	1	-	H	
799		2	2	1	-	H	
800		2	2	1	-	H	
801		2	2	1	-	H	
802		2	2	1	-	H	
803		2	2	1	-	H	

Table 1.7 4

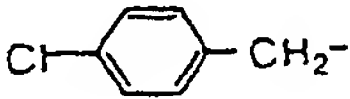
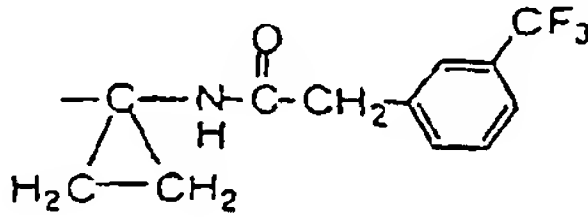
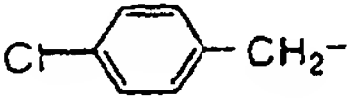
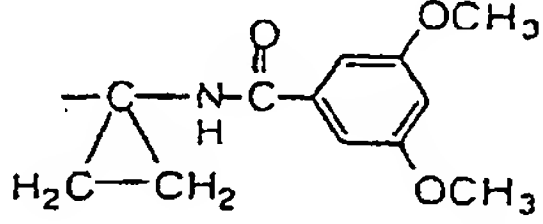
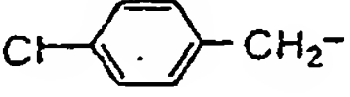
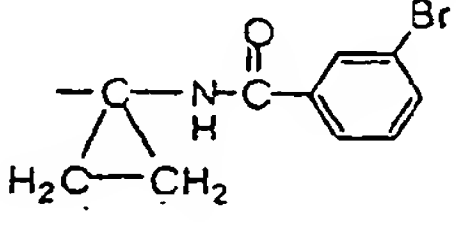
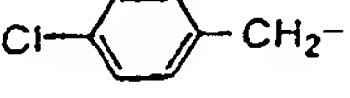
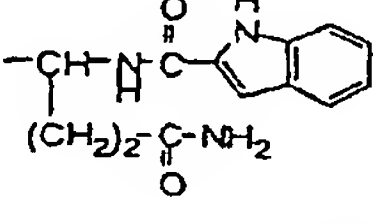

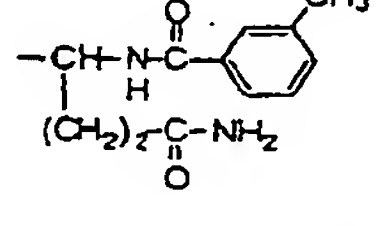
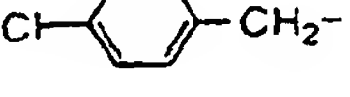
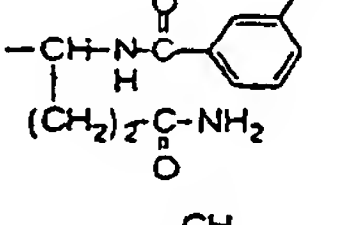

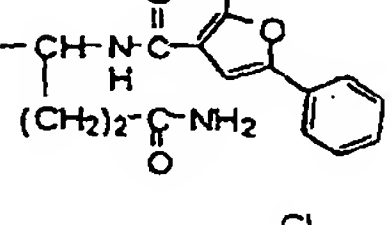
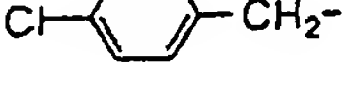
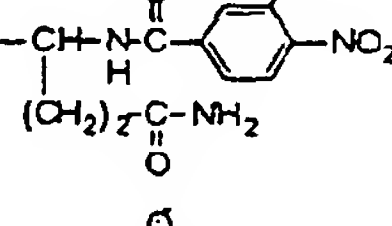
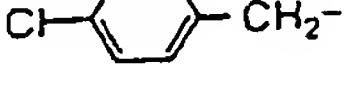
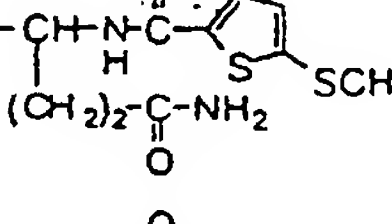

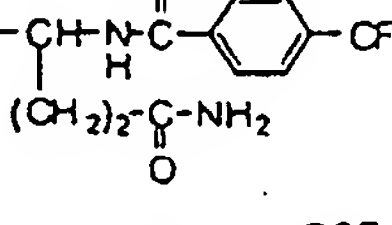
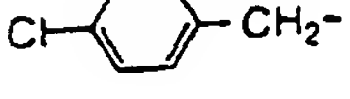
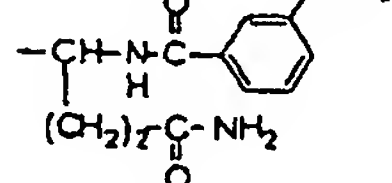
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_l -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
804		2	2	1	-	H	
805		2	2	1	-	H	
806		2	2	1	-	H	
807		2	2	1	-	H	
808		2	2	1	-	H	
809		2	2	1	-	H	
810		2	2	1	-	H	
811		2	2	1	-	H	
812		2	2	1	-	H	
813		2	2	1	-	H	
814		2	2	1	-	H	

Table 1.75


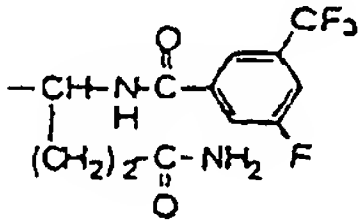

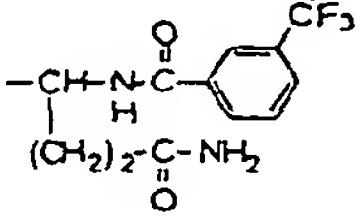
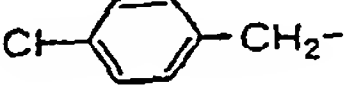
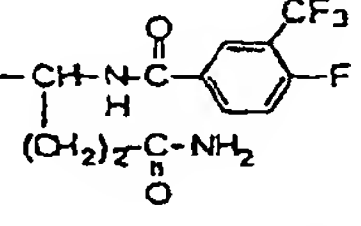
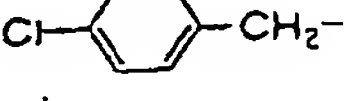
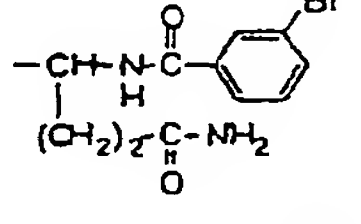
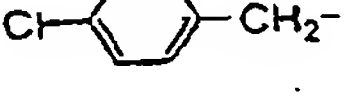
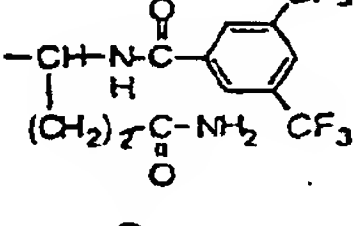
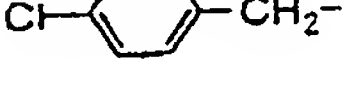
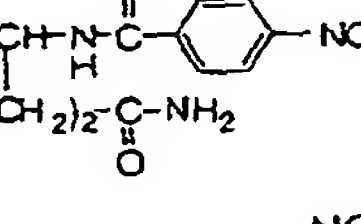
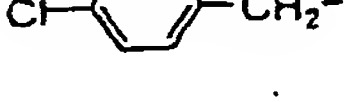
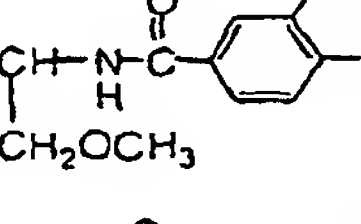

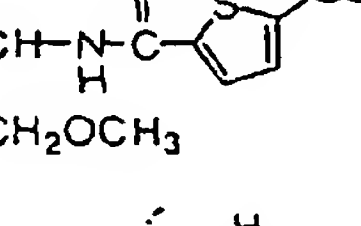

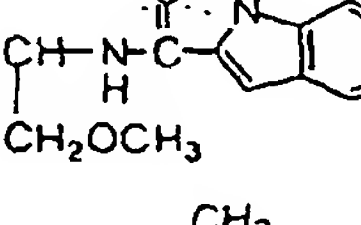

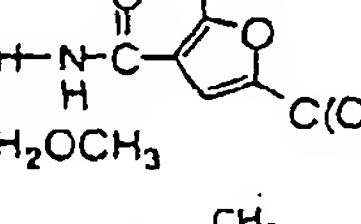
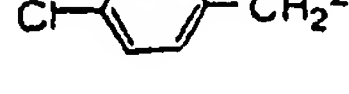
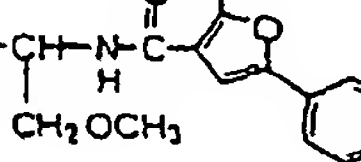
Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ R^2 \end{matrix} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
815		2	2	1	-	H	
816		2	2	1	-	H	
817		2	2	1	-	H	
818		2	2	1	-	H	
819		2	2	1	-	H	
820		2	2	1	-	H	
821		2	2	1	-	H	
822		2	2	1	-	H	
823		2	2	1	-	H	
824		2	2	1	-	H	
825		2	2	1	-	H	

Table 1.7 6

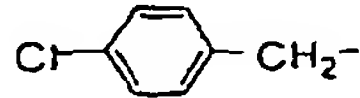
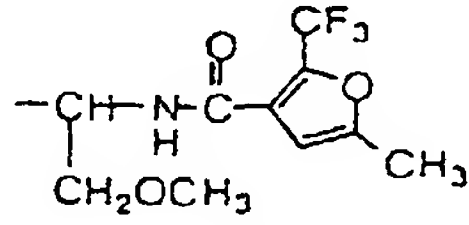

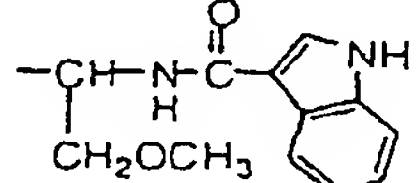

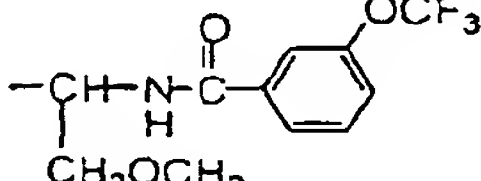
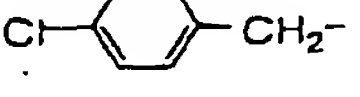
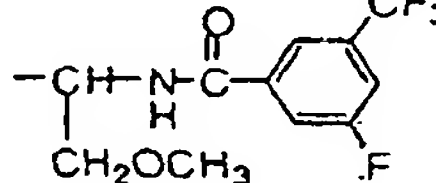
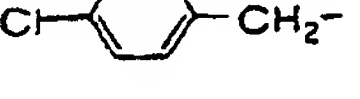
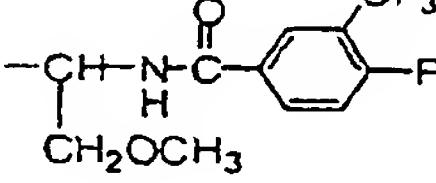
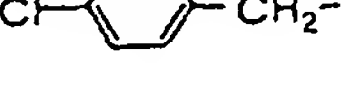
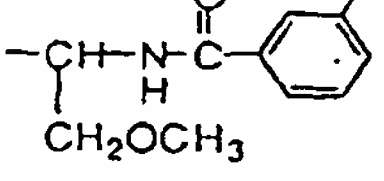

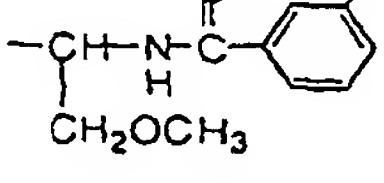

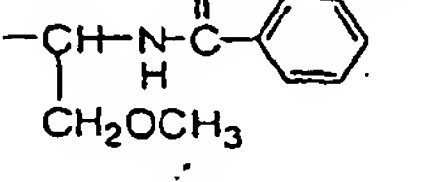

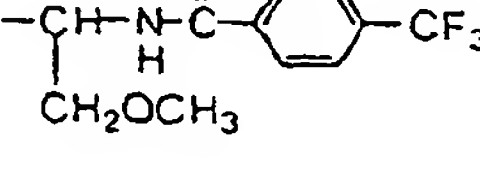
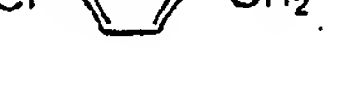
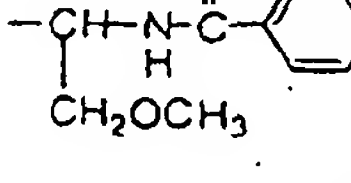
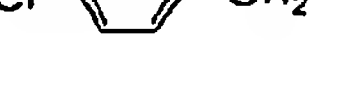
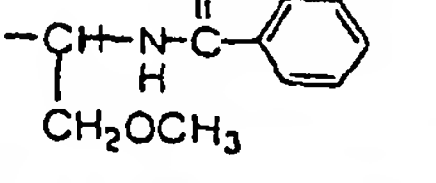
Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (CH_2)_j \text{---}$	k	m	n	chirality	R^3	$-(CH_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} \text{---} (CH_2)_q \text{---} G \text{---} R^6$
826		2	2	1	-	H	
827		2	2	1	-	H	
828		2	2	1	-	H	
829		2	2	1	-	H	
830		2	2	1	-	H	
831		2	2	1	-	H	
832		2	2	1	-	H	
833		2	2	1	-	H	
834		2	2	1	-	H	
835		2	2	1	-	H	
836		2	2	1	-	H	

Table 1.77

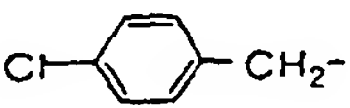
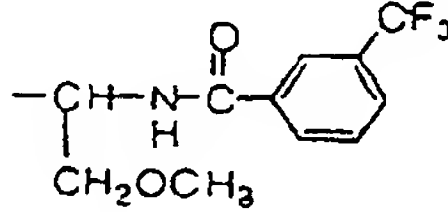
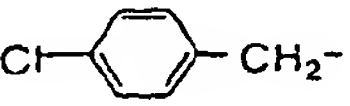
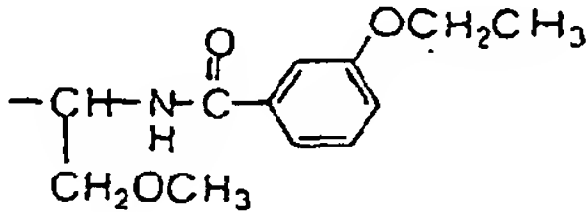
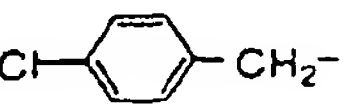
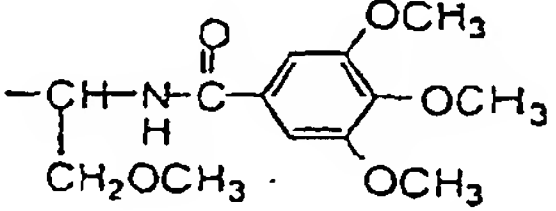
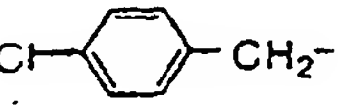
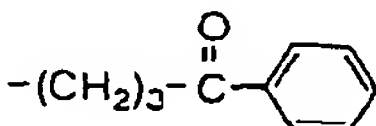
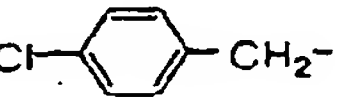
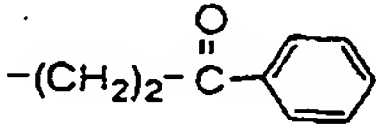
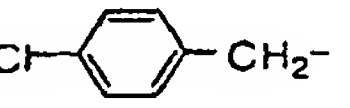
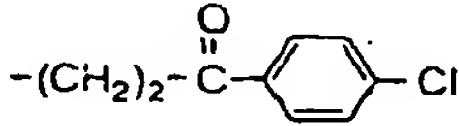
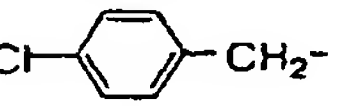
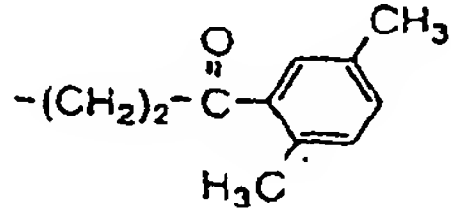
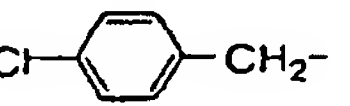
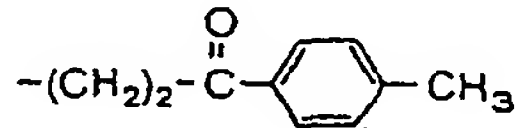
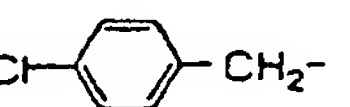
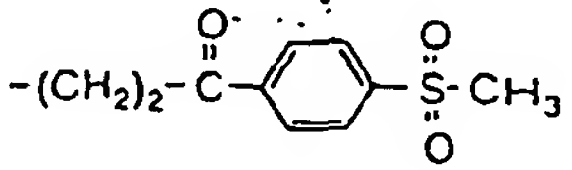
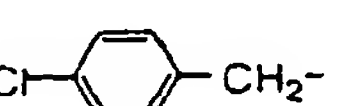
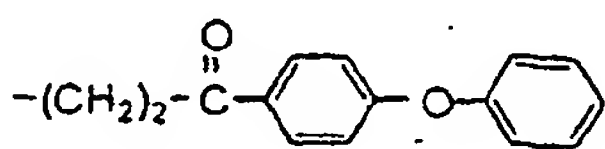

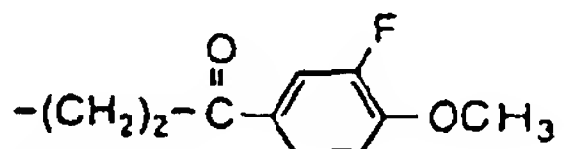
Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ (CH_2)_k \\ \diagdown \\ R^2 \end{matrix}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
837		2	2	1	-	H	
838		2	2	1	-	H	
839		2	2	1	-	H	
840		2	2	1	-	H	
841		2	2	1	-	H	
842		2	2	1	-	H	
843		2	2	1	-	H	
844		2	2	1	-	H	
845		2	2	1	-	H	
846		2	2	1	-	H	
847		2	2	1	-	H	

Table 1.78

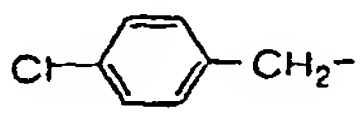
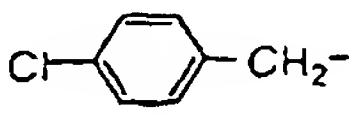
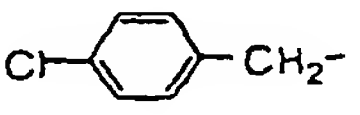
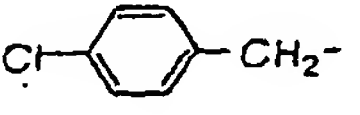

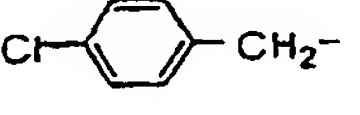
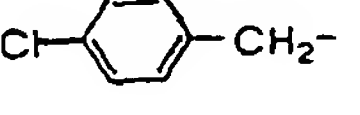
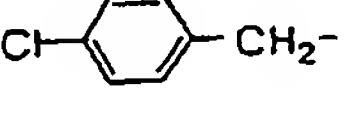
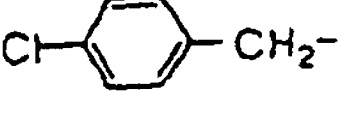
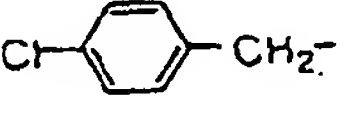
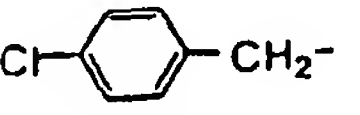
5	Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p-\overset{\overset{R^4}{ }}{\underset{\underset{R^5}{ }}{C}}-(CH_2)_q-G-R^6$
10	848		2	2	1	-	H	$-(CH_2)_2-\overset{\overset{O}{ }}{C}-\text{C}_6\text{H}_3(\text{CH}_3)_2$
15	849		2	2	1	-	H	$-(CH_2)_2-\overset{\overset{O}{ }}{C}-\text{C}_6\text{H}_2(\text{OCH}_3)_2$
20	850		2	2	1	-	H	$-\text{CH}_2-\overset{\overset{O}{ }}{\underset{\underset{O}{ }}{S}}-\text{C}_6\text{H}_4-\text{CH}_3$
25	851		2	2	1	-	H	$-\text{CH}_2-\text{NH}-\overset{\overset{O}{ }}{C}-\text{NH}-\text{C}_6\text{H}_4-\text{CF}_3$
30	852		2	2	1	-	H	$-\text{CH}_2-\text{NH}-\overset{\overset{O}{ }}{C}-\text{NH}-\text{C}_6\text{H}_4-\text{CF}_3$
35	853		2	2	1	-	H	$-\text{CH}_2-\text{NH}-\overset{\overset{O}{ }}{C}-\text{NH}-\text{C}_6\text{H}_5$
40	854		2	2	1	-	H	$-\text{CH}_2-\text{NH}-\overset{\overset{O}{ }}{C}-\text{NH}-\text{C}_6\text{H}_4-\text{CH}_3$
45	855		2	2	1	-	H	$-\text{CH}_2-\text{NH}-\overset{\overset{O}{ }}{C}-\text{NH}-\text{C}_6\text{H}_4-\text{CH}_3$
50	856		2	2	1	-	H	$-\text{CH}_2-\text{NH}-\overset{\overset{O}{ }}{C}-\text{NH}-\text{C}_6\text{H}_3(\text{O}-\text{C}(=\text{O})\text{CH}_3)_2$
55	857		2	2	1	-	H	$-\text{CH}_2-\text{NH}-\overset{\overset{O}{ }}{C}-\text{NH}-\text{C}_6\text{H}_4-\text{OCH}_3$
	858		2	2	1	-	H	$-\text{CH}_2-\text{NH}-\overset{\overset{O}{ }}{C}-\text{NH}-\text{C}_6\text{H}_4-\text{OCH}_3$

Table 1.7 9

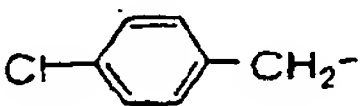
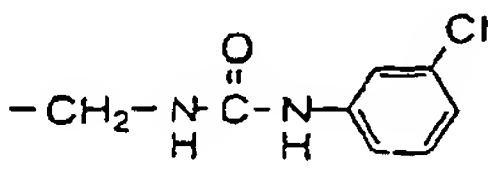
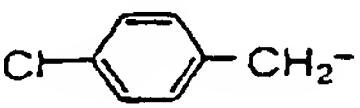
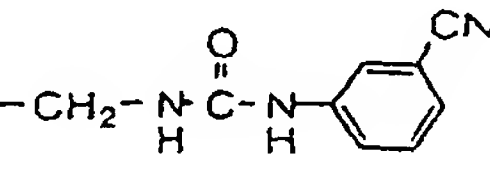
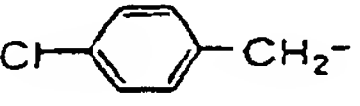
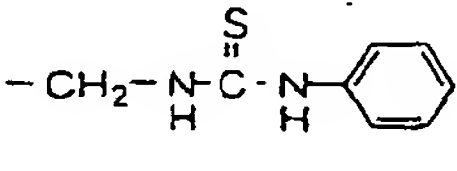
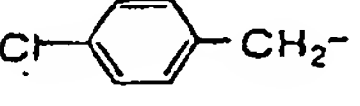
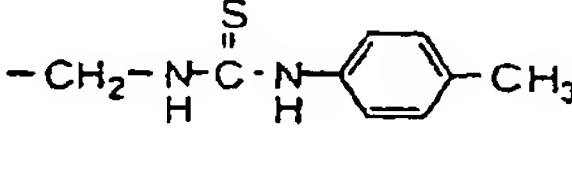

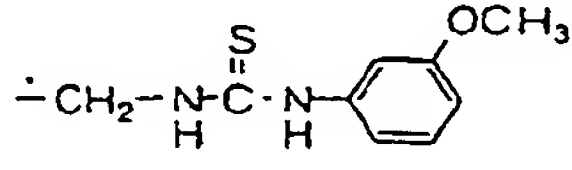
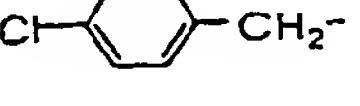
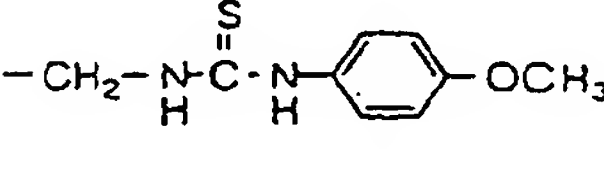
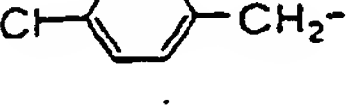
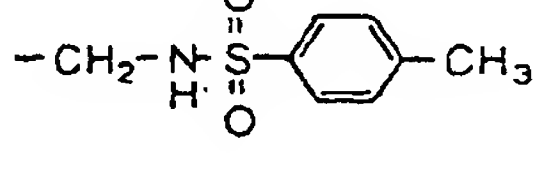
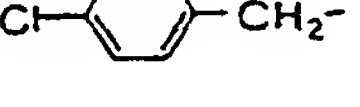
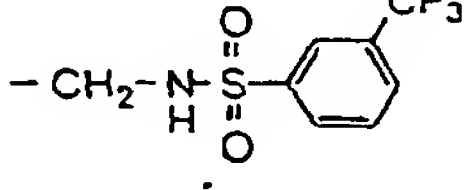
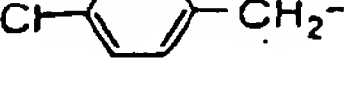
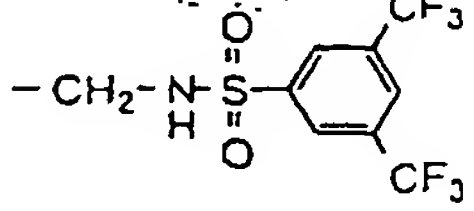

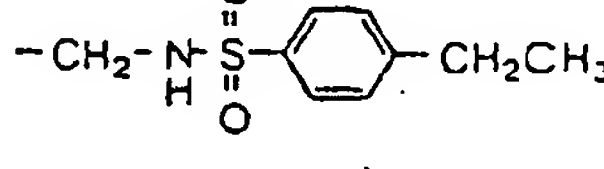

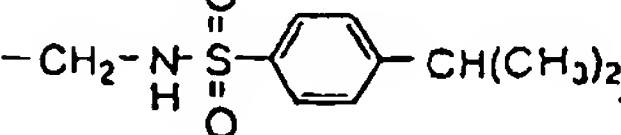
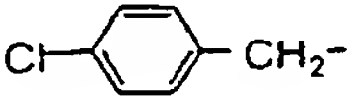
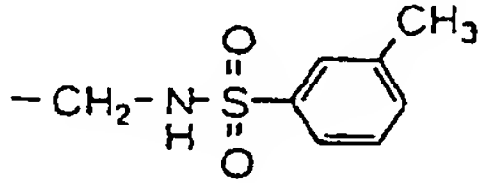
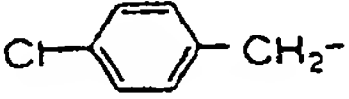
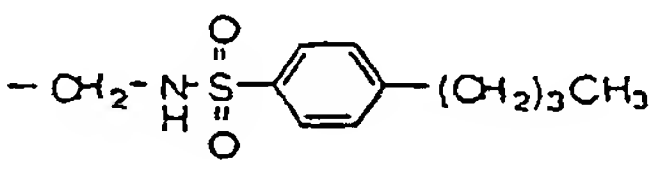

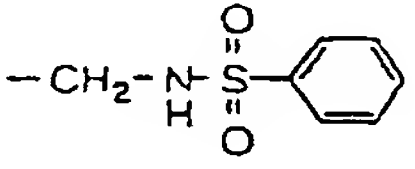

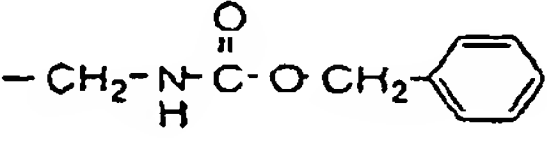
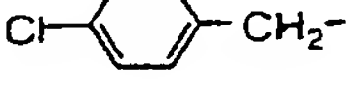
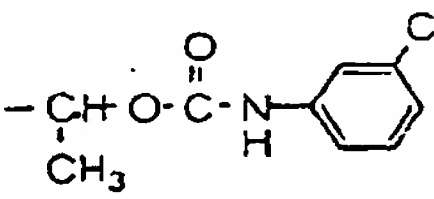
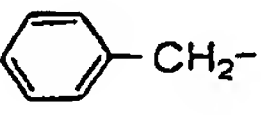
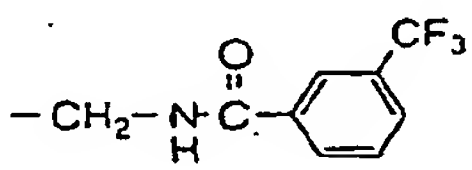
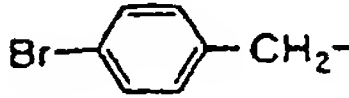
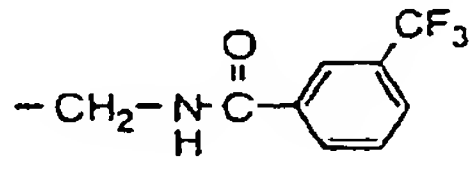

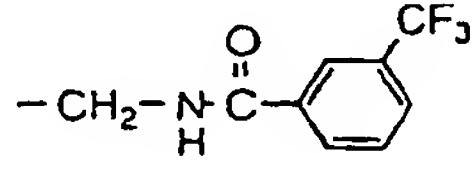

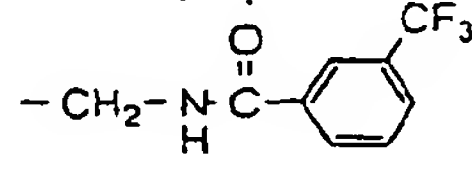
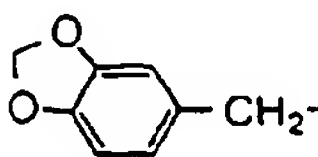
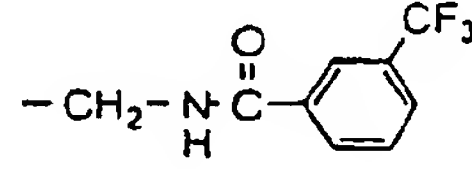
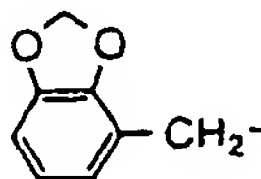
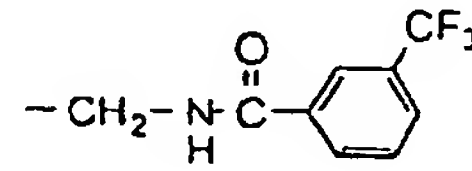
Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ (CH_2)_j \\ \diagdown \\ R^2 \end{matrix}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
859		2	2	1	-	H	
860		2	2	1	-	H	
861		2	2	1	-	H	
862		2	2	1	-	H	
863		2	2	1	-	H	
864		2	2	1	-	H	
865		2	2	1	-	H	
866		2	2	1	-	H	
867		2	2	1	-	H	
868		2	2	1	-	H	
869		2	2	1	-	H	

Table 1.80

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_i- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
870		2	2	1	-	H	
871		2	2	1	-	H	
872		2	2	1	-	H	
873		2	2	1	-	H	
874		2	2	1	-	H	
875		2	2	1	-	H	
876		2	2	1	-	H	
877		2	2	1	-	H	
878		2	2	1	-	H	
879		2	2	1	-	H	
880		2	2	1	-	H	

07-1

Table 1.8 1

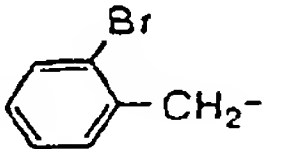
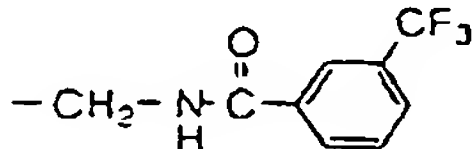
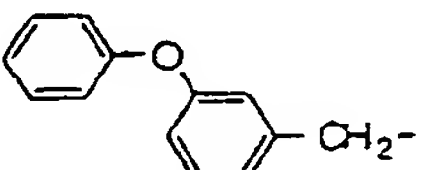
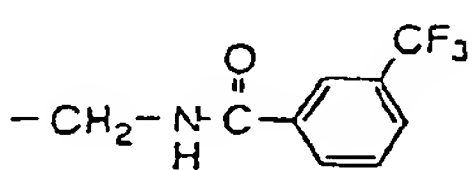
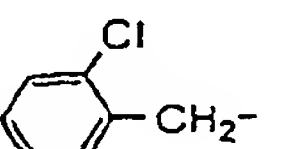
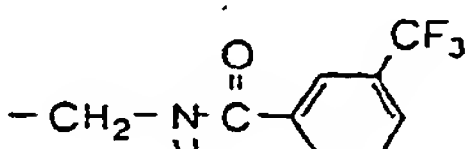
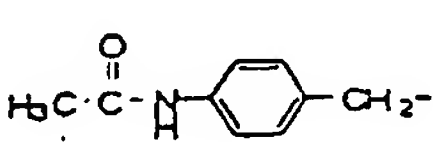
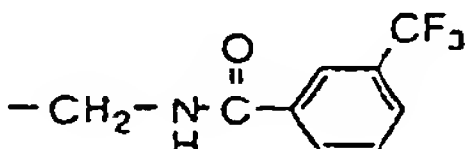
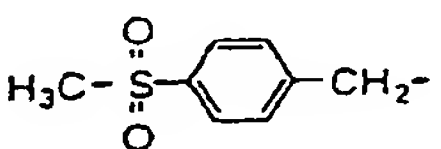
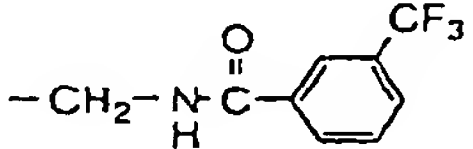
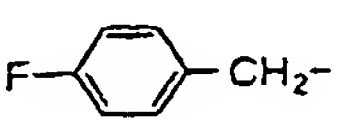
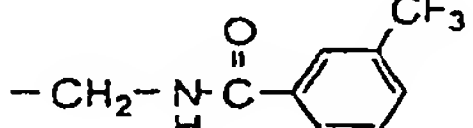
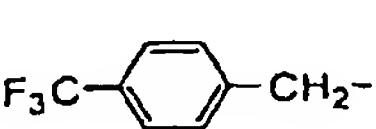
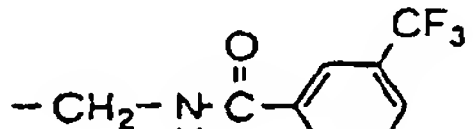
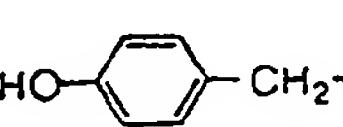
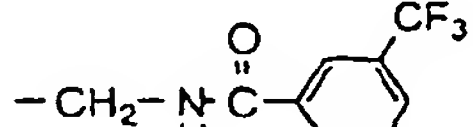
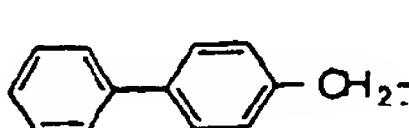
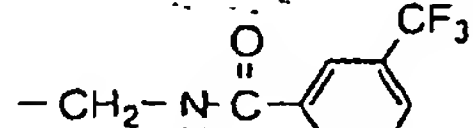
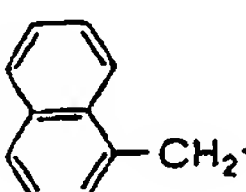
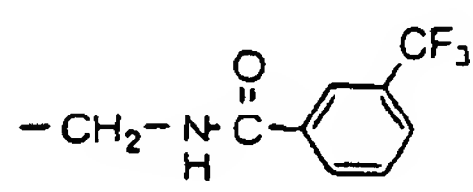
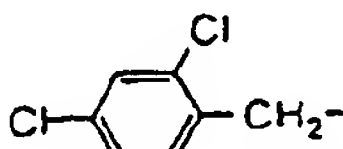
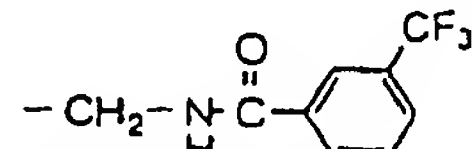
5 Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
10 881		2	2	1	-	H	
15 882		2	2	1	-	H	
20 883		2	2	1	-	H	
25 884		2	2	1	-	H	
30 885		2	2	1	-	H	
35 886		2	2	1	-	H	
40 887		2	2	1	-	H	
45 888		2	2	1	-	H	
50 889		2	2	1	-	H	
55 890		2	2	1	-	H	
891		2	2	1	-	H	

Table 1.82

Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ R^2 \end{matrix} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
892		2	2	1	-	H	
893		2	2	1	-	H	
894		2	2	1	-	H	
895		2	2	1	-	H	
896		2	2	1	-	H	
897		2	2	1	-	H	
898		2	2	1	-	H	
899		2	2	1	-	H	
900		2	2	1	-	H	
901		2	2	1	-	H	
902		2	2	1	-	H	

Table 1.8 3

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_l -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
903		2	2	1	-	H	
904		2	2	1	-	H	
905		2	2	1	-	H	
906		2	2	1	-	H	
907		2	2	1	-	H	
908		2	2	1	-	H	
909		2	2	1	-	H	
910		2	2	1	-	H	
911		2	2	1	-	H	
912		2	2	1	-	H	
913		2	2	1	-	H	

Table 1.8 4

5	Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (CH_2)_l \text{---}$	k	m	n	chirality	R^3	$-(CH_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} \text{---} (CH_2)_q \text{---} G \text{---} R^6$
10	914		2	2	1	-	H	
15	915		2	2	1	-	H	
20	916		2	2	1	-	H	
25	917		2	2	1	-	H	
30	918		2	2	1	-	H	
35	919		2	2	1	-	H	
40	920		2	2	1	-	H	
45	921		2	2	1	-	H	
50	922		2	2	1	-	H	
55	923		2	2	1	-	H	
	924		2	2	1	-	H	

Table 1.85

5 Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
10 925	$H_2N-C(=O)-C_6H_4-CH_2-$	2	2	1	-	H	$-CH_2-NH-C(=O)-C_6H_4-CF_3$
15 926	$C_6H_5-CH_2-C_6H_4-CH_2-$	2	2	1	-	H	$-CH_2-NH-C(=O)-C_6H_4-CF_3$
20 927	$F_3CO-C_6H_4-CH_2-$	2	2	1	-	H	$-CH_2-NH-C(=O)-C_6H_4-CF_3$
25 928	$F_3CO-C_6H_4-CH_2-$	2	2	1	-	H	$-CH_2-NH-C(=O)-C_6H_4-CF_3$
30 929	$H_3CS-C_6H_4-CH_2-$	2	2	1	-	H	$-CH_2-NH-C(=O)-C_6H_4-CF_3$
35 930	$CH_3-C_6H_4-CH_2-$	2	2	1	-	H	$-CH_2-NH-C(=O)-C_6H_4-CF_3$
40 931	$NC-C_6H_4-CH_2-$	2	2	1	-	H	$-CH_2-NH-C(=O)-C_6H_4-CF_3$
45 932	$NO_2-C_6H_3(Cl)-CH_2-$	2	2	1	-	H	$-CH_2-NH-C(=O)-C_6H_4-CF_3$
50 933	$CH_3-CH(C_6H_5)-$	2	2	1	-	H	$-CH_2-NH-C(=O)-C_6H_4-CF_3$
55 934	$C_5H_5N-CH_2-$	2	2	1	-	H	$-CH_2-NH-C(=O)-C_6H_4-CF_3$
935	$O_2N-C_6H_4-CH_2-$	2	2	1	-	H	$-CH_2-NH-C(=O)-C_6H_4-CF_3$

Table 1.8 6

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_k \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
936		2	2	1	-	H	
937		2	2	1	-	H	
938		2	2	1	-	H	
939		2	2	1	-	H	
940		2	2	1	-	H	
941		2	2	1	-	H	
942		2	2	1	-	H	
943		1	4	0	-	H	
944		1	4	0	-	H	
945		1	4	0	-	H	
946		1	4	0	-	H	

Table 1.87


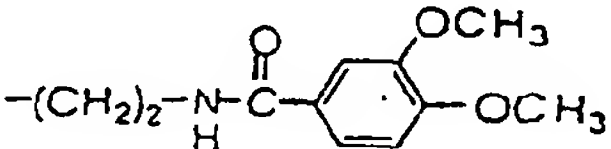
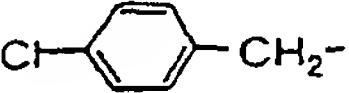
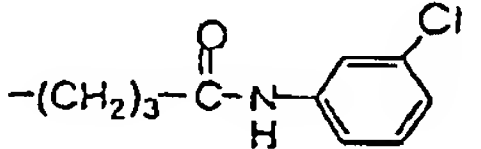
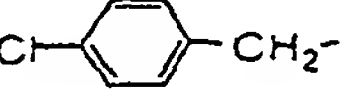
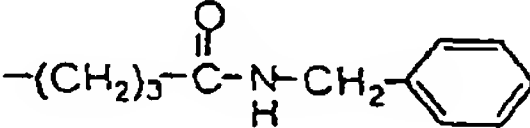
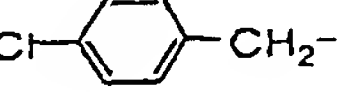
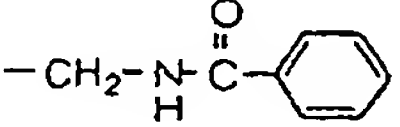
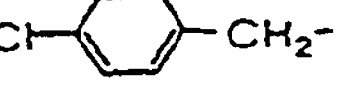
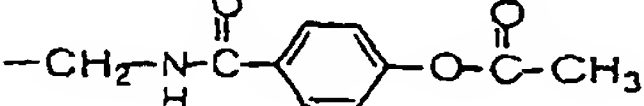
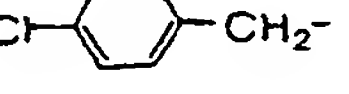
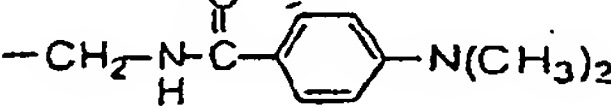
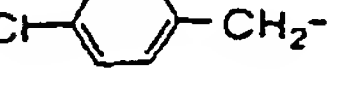
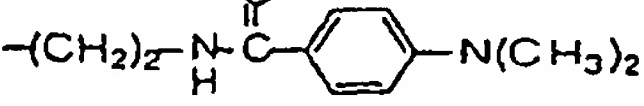
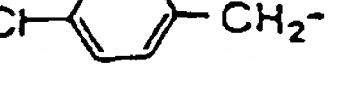
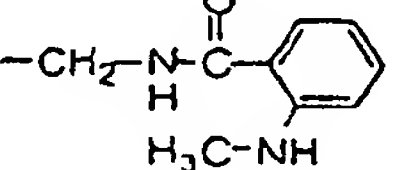
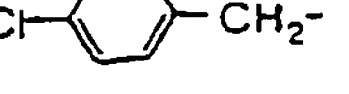
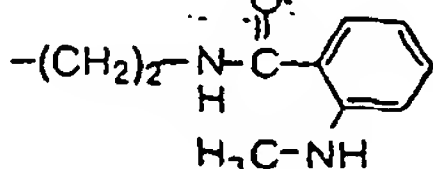
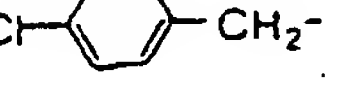
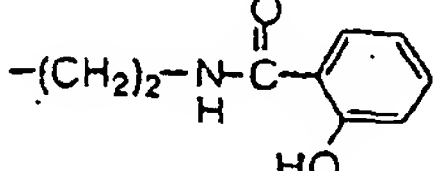
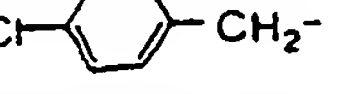
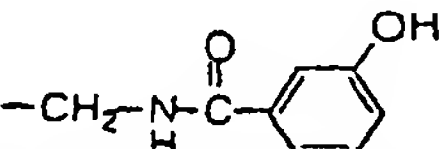
Compd. No.	$\begin{array}{c} R^1 \\ \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
947		1	4	0	-	H	
948		1	4	0	-	H	
949		1	4	0	-	H	
950		0	4	1	-	H	
951		1	2	0	R	H	
952		1	2	0	R	H	
953		1	2	0	R	H	
954		1	2	0	R	H	
955		1	2	0	R	H	
956		1	2	0	R	H	
957		1	2	0	R	H	

Table 1.88

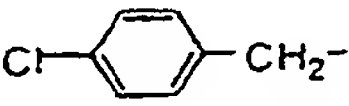
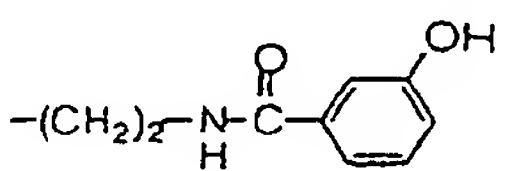

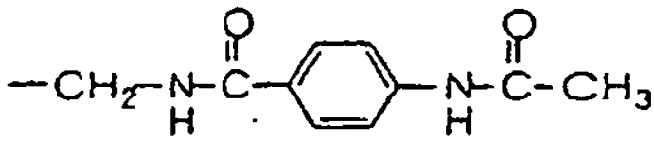
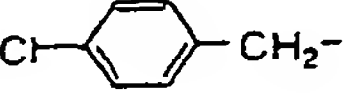
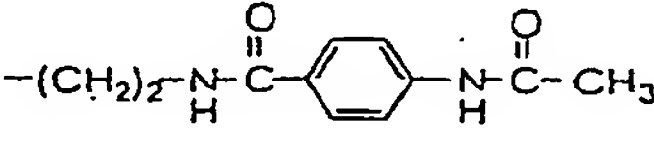
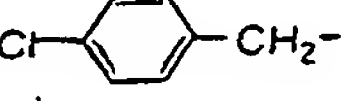
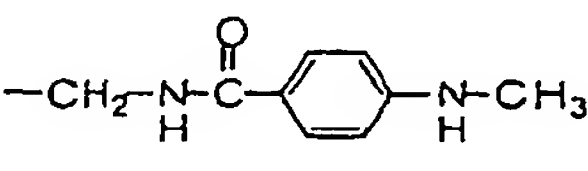
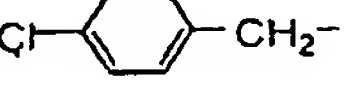
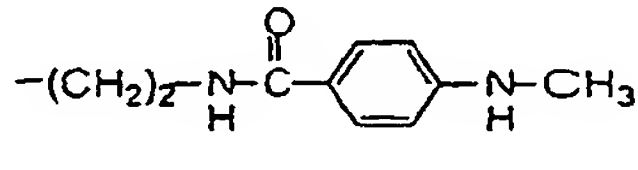
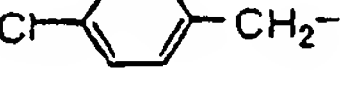
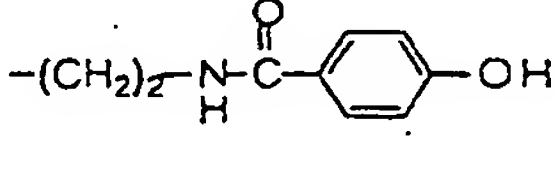
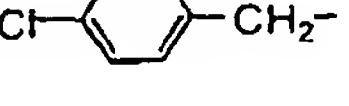
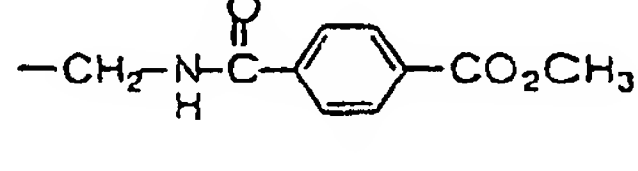
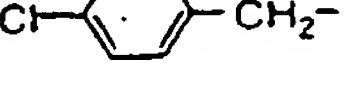
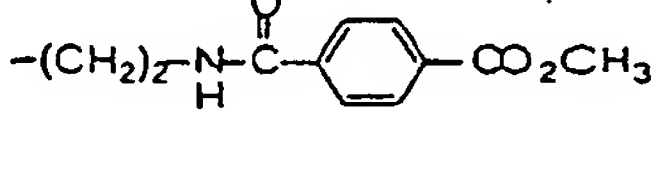
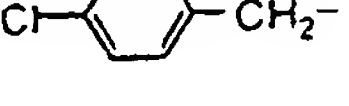
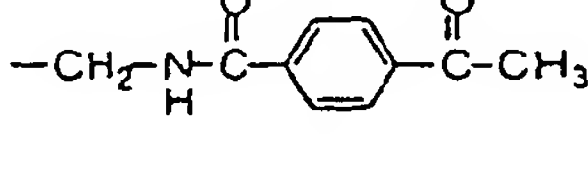

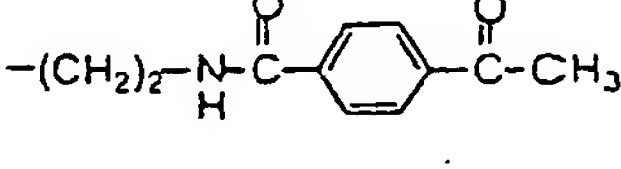
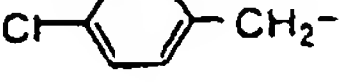
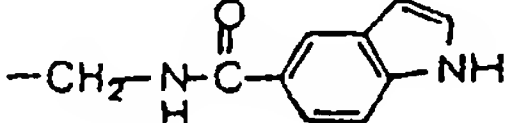
Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ R^2 \end{matrix} (CH_2)_l$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
958		1	2	0	R	H	
959		1	2	0	R	H	
960		1	2	0	R	H	
961		1	2	0	R	H	
962		1	2	0	R	H	
963		1	2	0	R	H	
964		1	2	0	R	H	
965		1	2	0	R	H	
966		1	2	0	R	H	
967		1	2	0	R	H	
968		1	2	0	R	H	

Table 1.89

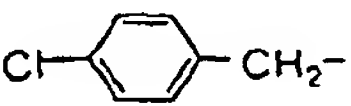
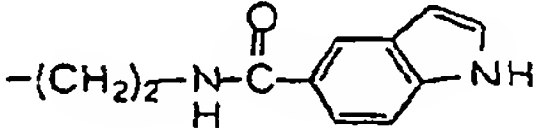
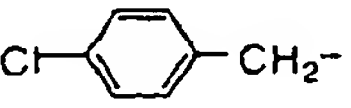
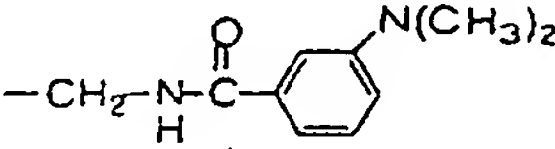
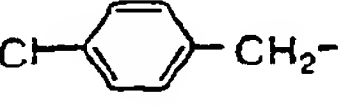
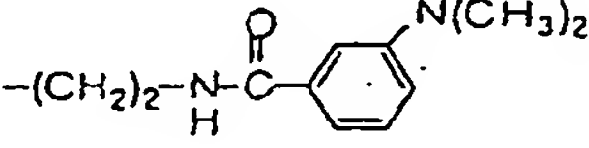
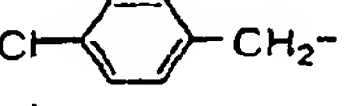
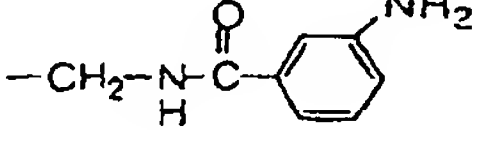
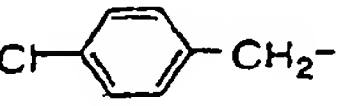
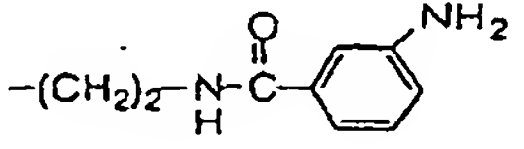
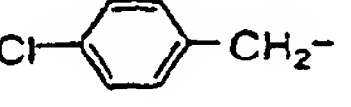
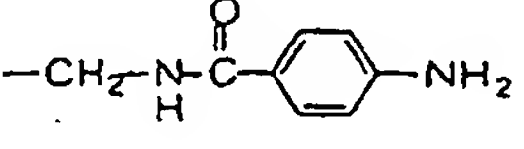
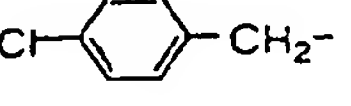
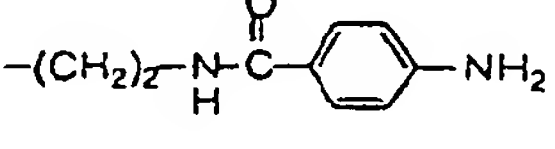
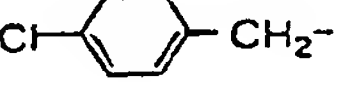
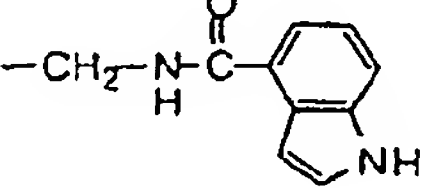
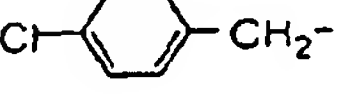
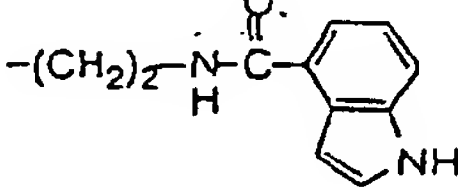
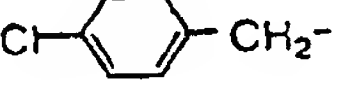
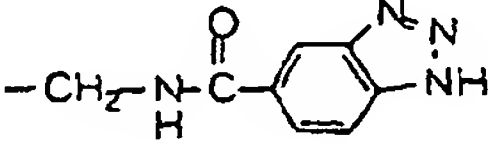
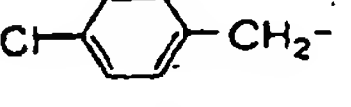
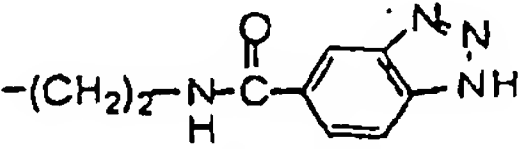
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ -C- \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
969		1	2	0	R	H	
970		1	2	0	R	H	
971		1	2	0	R	H	
972		1	2	0	R	H	
973		1	2	0	R	H	
974		1	2	0	R	H	
975		1	2	0	R	H	
976		1	2	0	R	H	
977		1	2	0	R	H	
978		1	2	0	R	H	
979		1	2	0	R	H	

Table 1.90

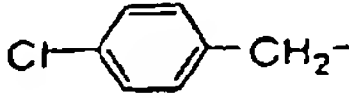
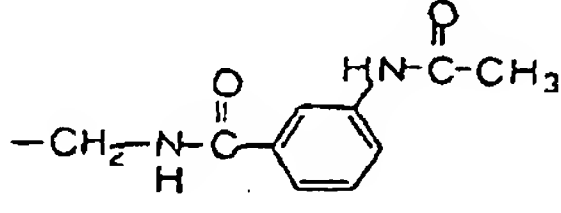

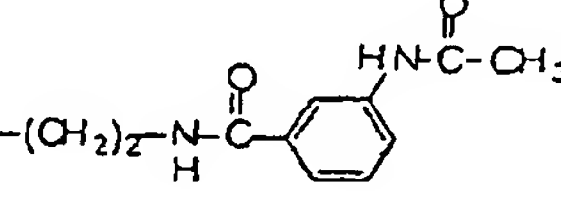

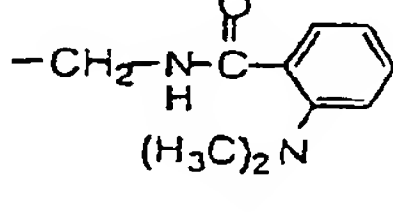
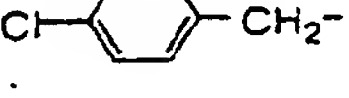
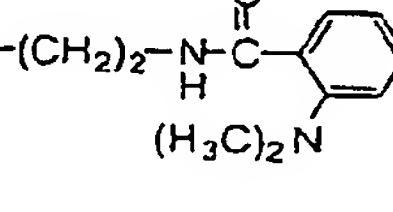
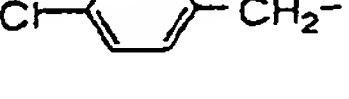
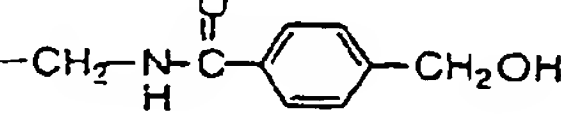

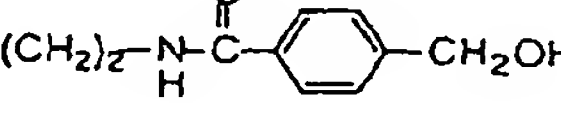
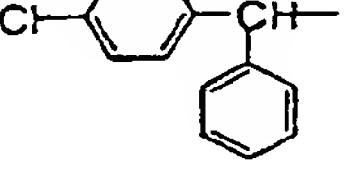
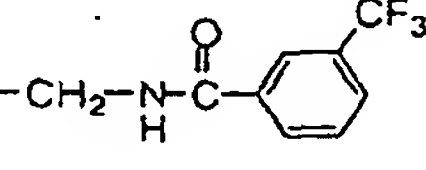
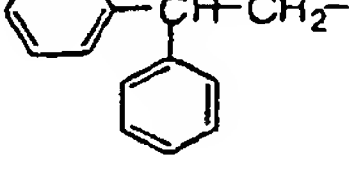
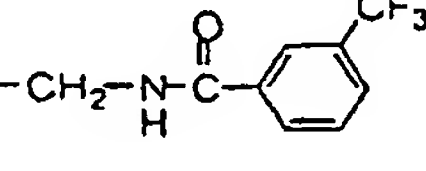
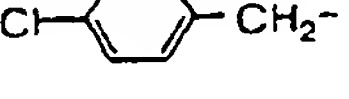
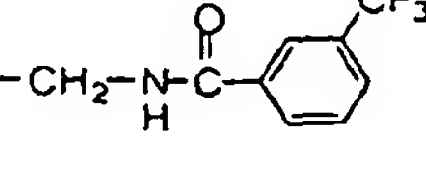

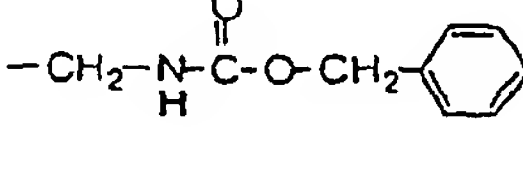

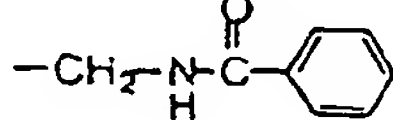
5 Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
10 980		1	2	0	R	H	
15 981		1	2	0	R	H	
20 982		1	2	0	R	H	
25 983		1	2	0	R	H	
30 984		1	2	0	R	H	
35 985		1	2	0	R	H	
40 986		1	2	0	R	H	
45 987		2	2	1	-	H	
50 988		1	4	0	-	H	
55 989		1	4	0	-	H	
990		1	4	0	-	H	

Table 1.9 1

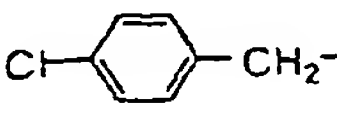
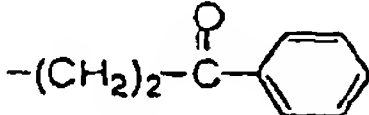
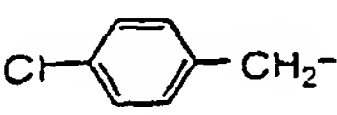

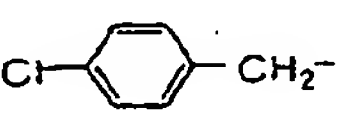
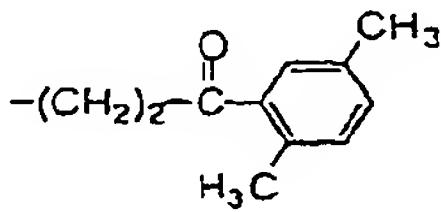
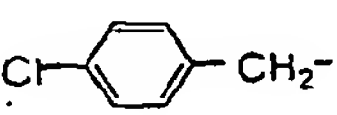
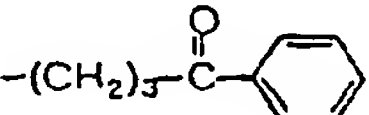
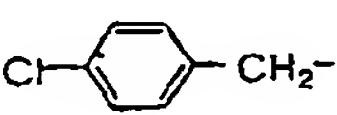
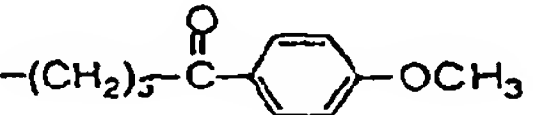
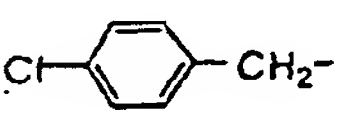
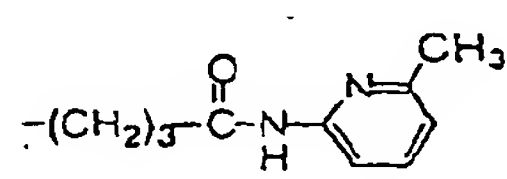
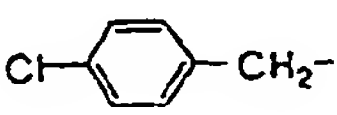
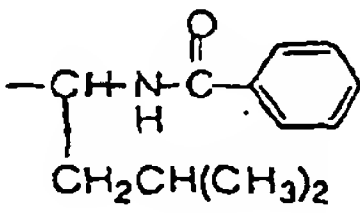
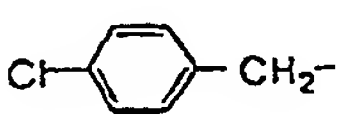
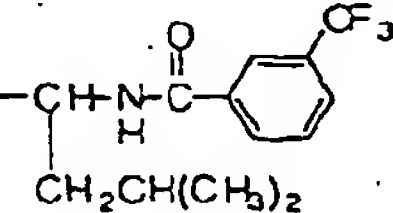
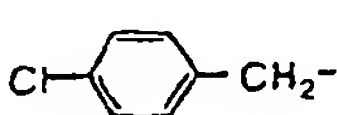
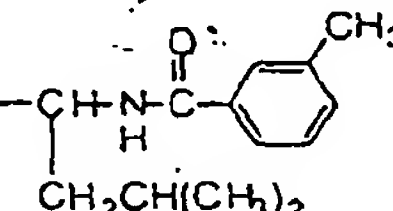
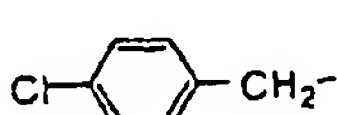
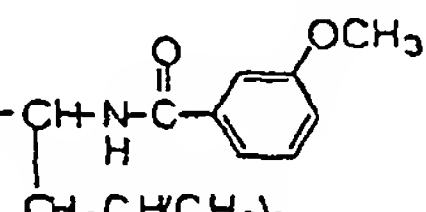

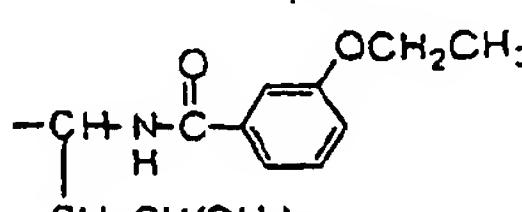
Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ R^2 \end{matrix} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
991		1	4	0	-	H	
992		1	4	0	-	H	
993		1	4	0	-	H	
994		1	4	0	-	H	
995		1	4	0	-	H	
996		1	4	0	-	H	
997		2	2	1	-	H	
998		2	2	1	-	H	
999		2	2	1	-	H	
1000		2	2	1	-	H	
1001		2	2	1	-	H	

Table 1.92

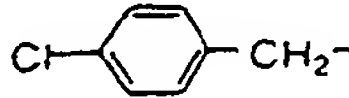
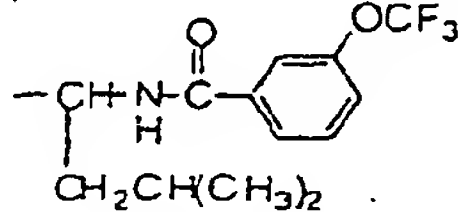
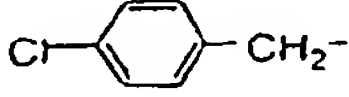
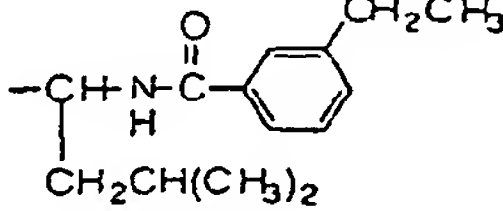
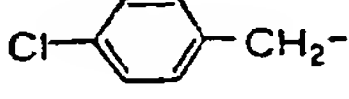
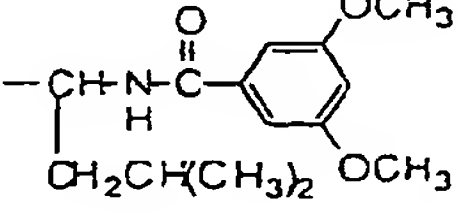
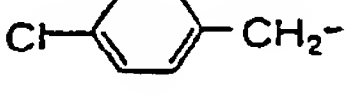
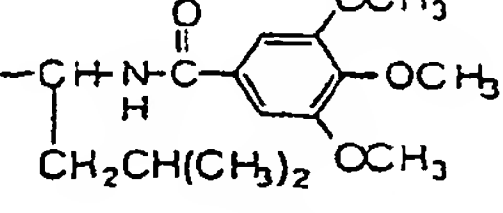
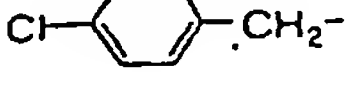
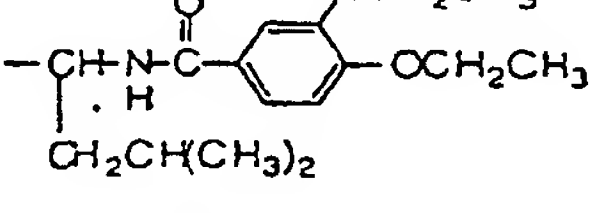
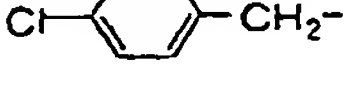
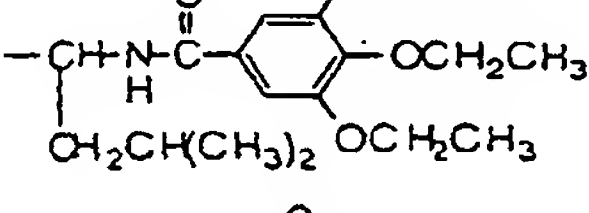
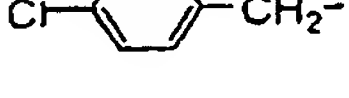
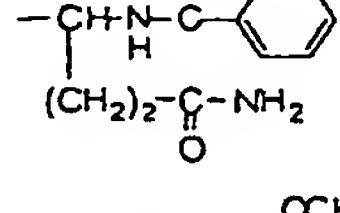

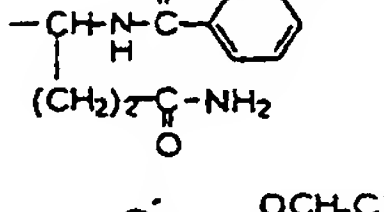

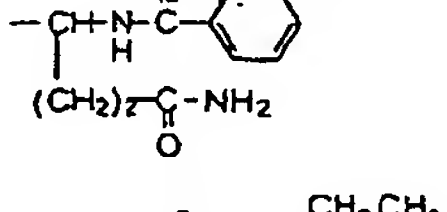

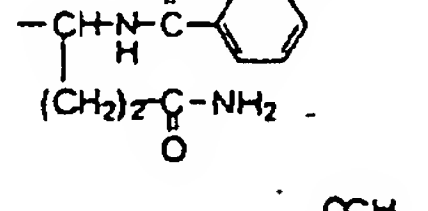
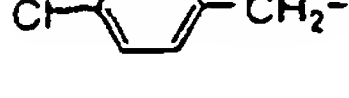
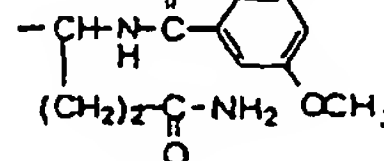
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1002		2	2	1	-	H	
1003		2	2	1	-	H	
1004		2	2	1	-	H	
1005		2	2	1	-	H	
1006		2	2	1	-	H	
1007		2	2	1	-	H	
1008		2	2	1	-	H	
1009		2	2	1	-	H	
1010		2	2	1	-	H	
1011		2	2	1	-	H	
1012		2	2	1	-	H	

Table 1.93

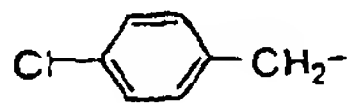
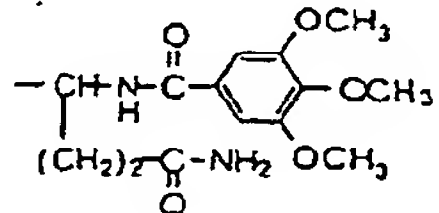
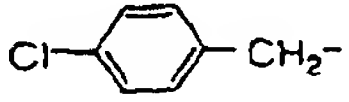
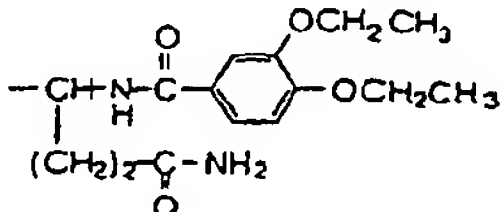
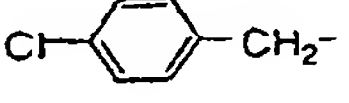
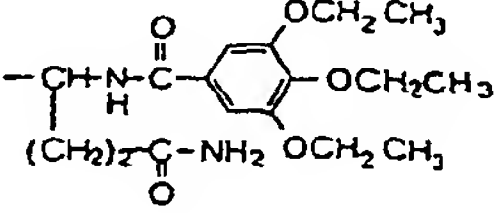
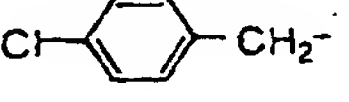
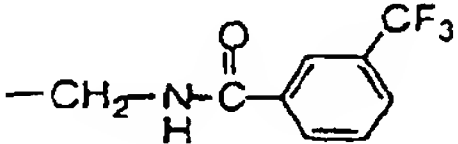
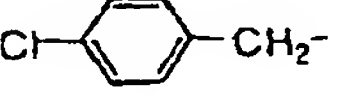
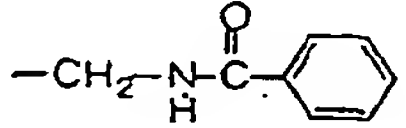
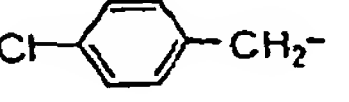
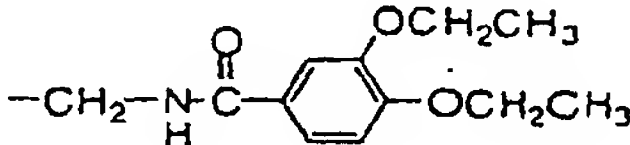

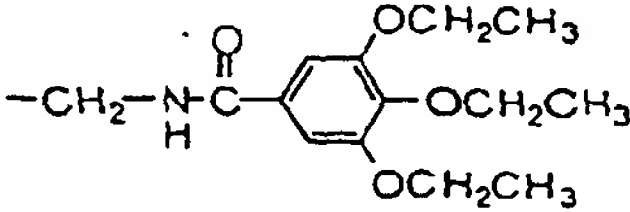
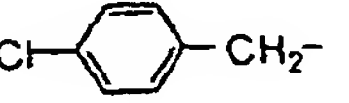
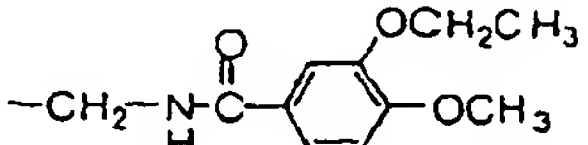
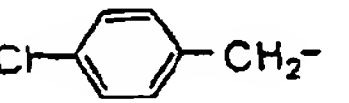
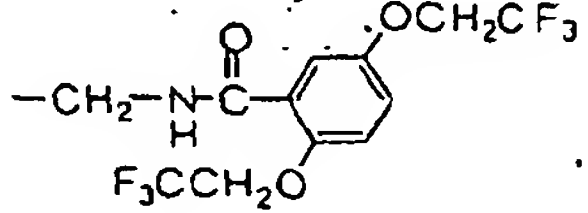
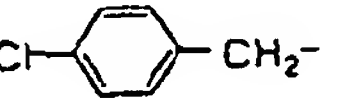
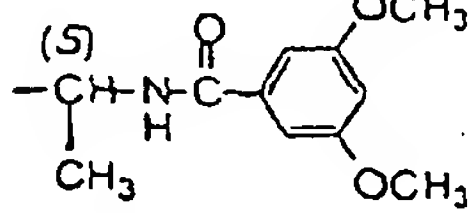
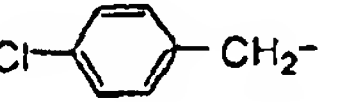
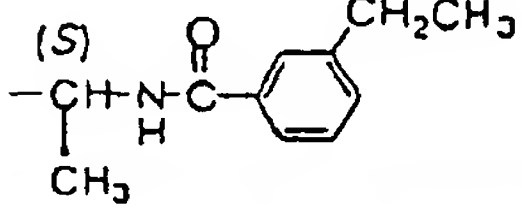
Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ R^2 \end{matrix} (CH_2)_l$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
1013		2	2	1	-	H	
1014		2	2	1	-	H	
1015		2	2	1	-	H	
1016		2	2	0	-	H	
1017		2	2	0	-	H	
1018		2	2	1	-	H	
1019		2	2	1	-	H	
1020		2	2	1	-	H	
1021		2	2	1	-	H	
1022		2	2	1	-	H	
1023		2	2	1	-	H	

Table 1.9 4


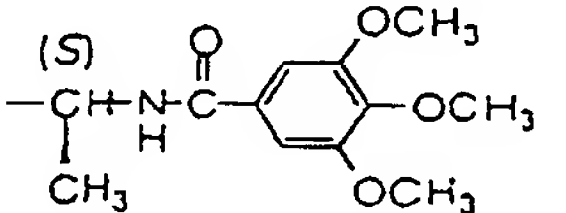
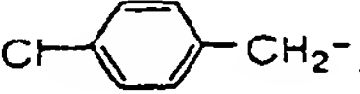
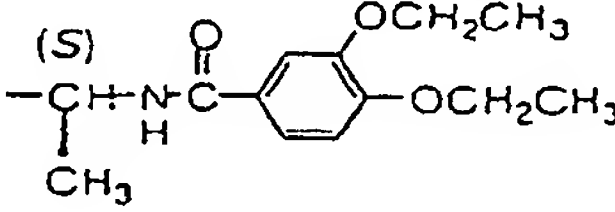
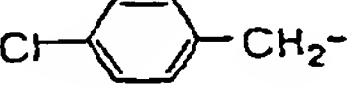
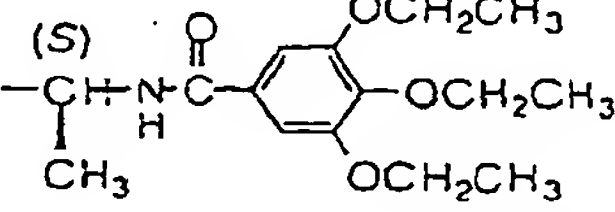
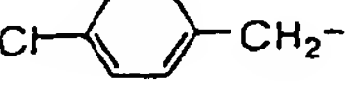
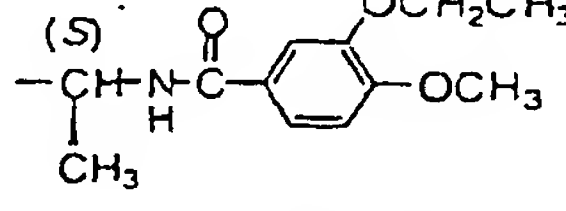
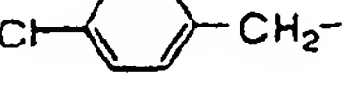
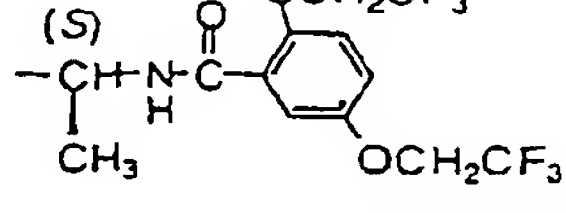

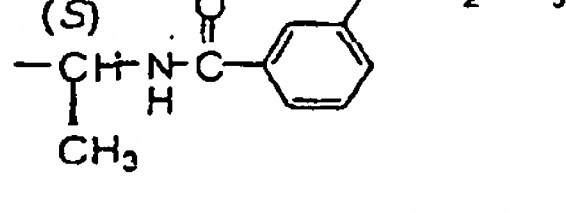
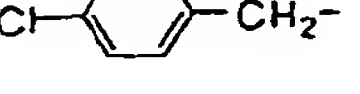
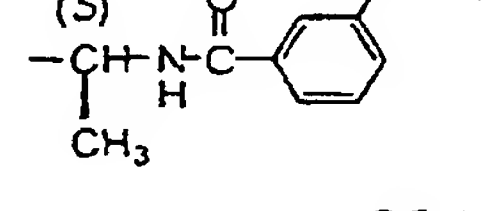
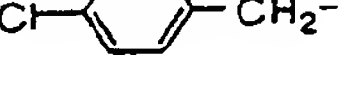
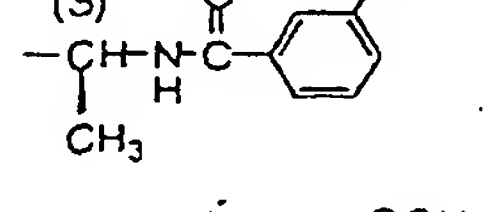
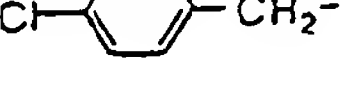
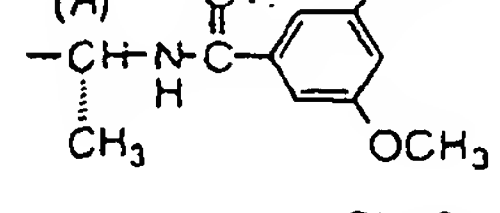

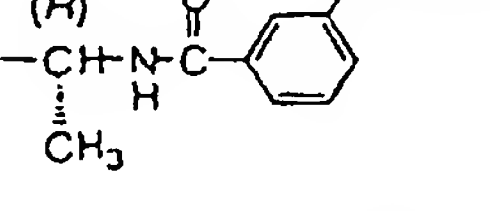

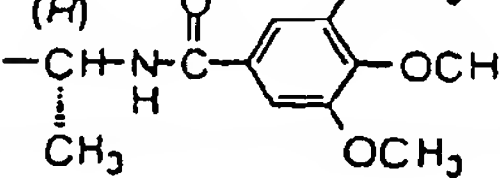
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1024		2	2	1	-	H	
1025		2	2	1	-	H	
1026		2	2	1	-	H	
1027		2	2	1	-	H	
1028		2	2	1	-	H	
1029		2	2	1	-	H	
1030		2	2	1	-	H	
1031		2	2	1	-	H	
1032		2	2	1	-	H	
1033		2	2	1	-	H	
1034		2	2	1	-	H	

Table 1.95

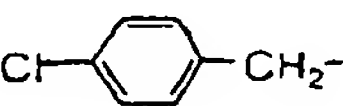
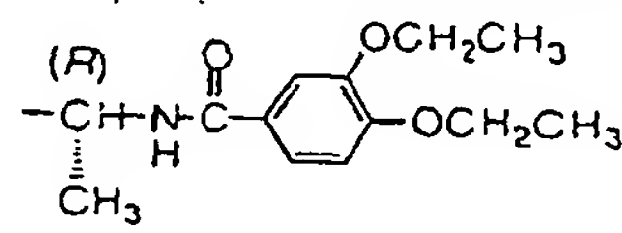

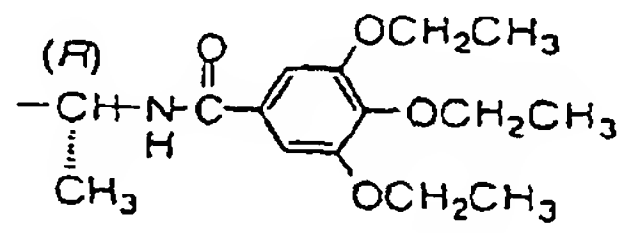
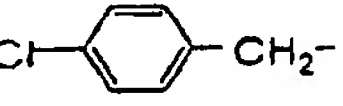
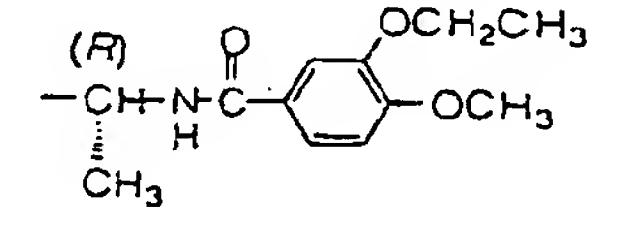
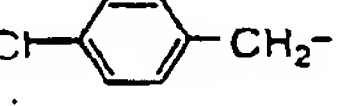
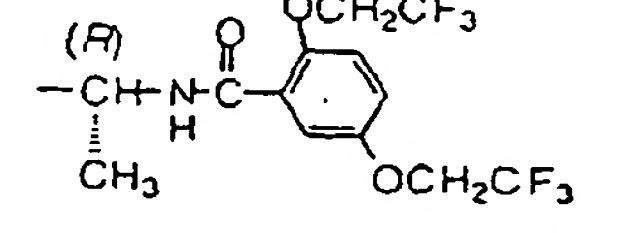
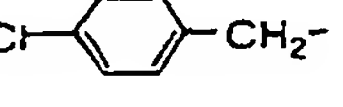
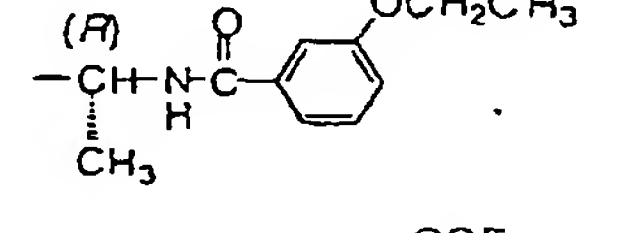
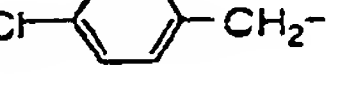
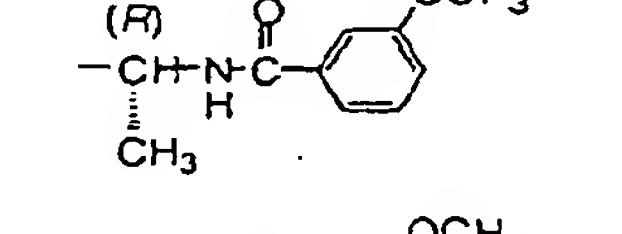
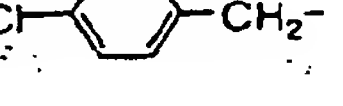
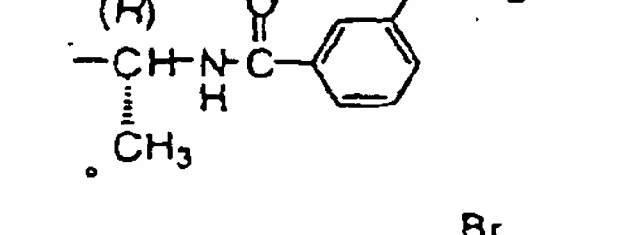
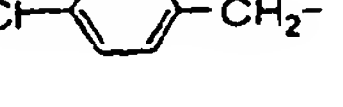
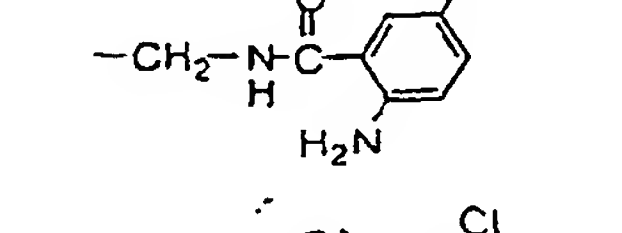
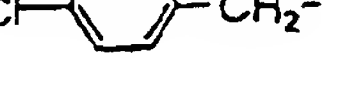
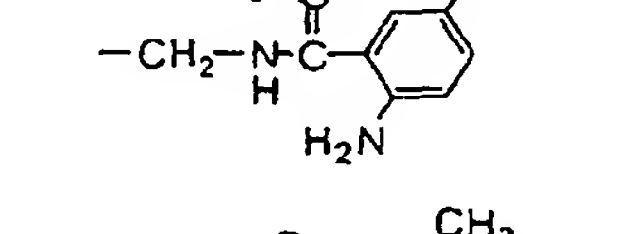
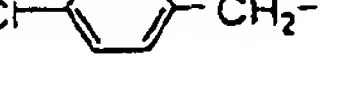
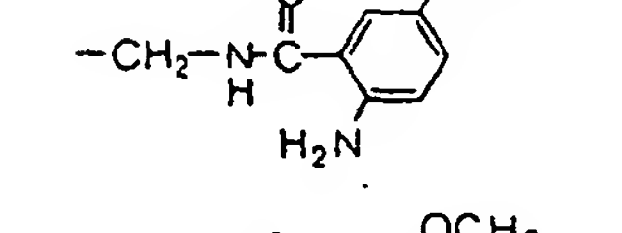
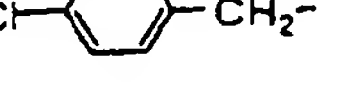
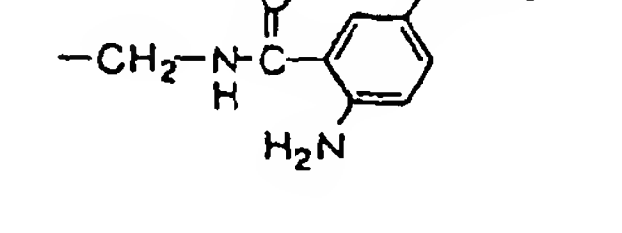
Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (\text{CH}_2)_j \text{---}$	k	m	n	chirality	R^3	$\text{---} (\text{CH}_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} \text{---} (\text{CH}_2)_q \text{---} \text{G---} R^6$
1035		2	2	1	-	H	
1036		2	2	1	-	H	
1037		2	2	1	-	H	
1038		2	2	1	-	H	
1039		2	2	1	-	H	
1040		2	2	1	-	H	
1041		2	2	1	-	H	
1042		2	2	1	-	H	
1043		2	2	1	-	H	
1044		2	2	1	-	H	
1045		2	2	1	-	H	

Table 1.96

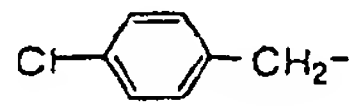
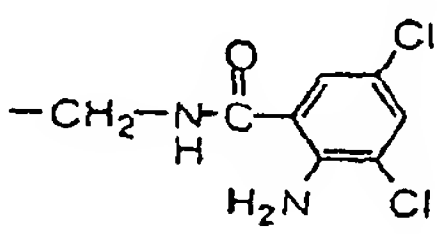
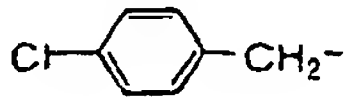
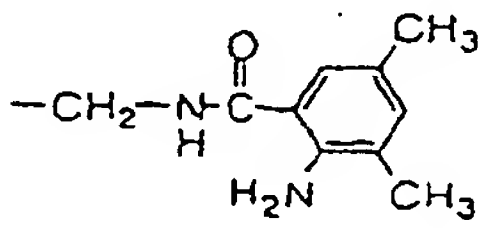
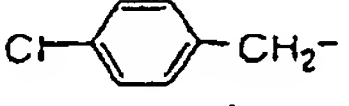
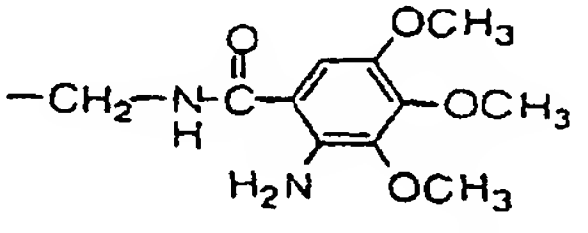
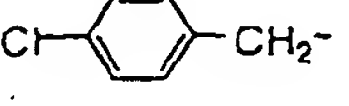
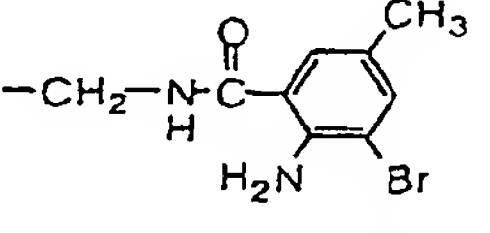
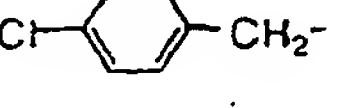
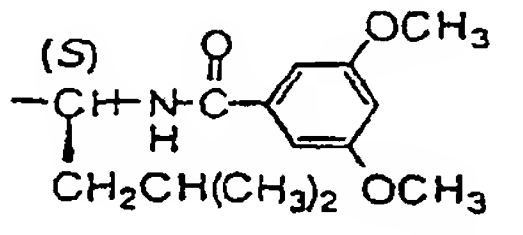
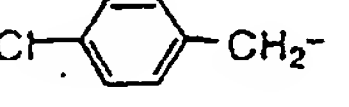
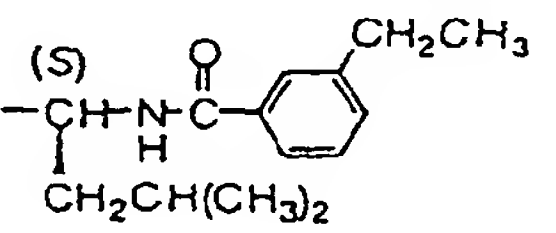
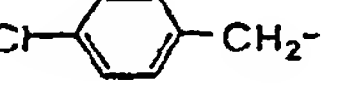
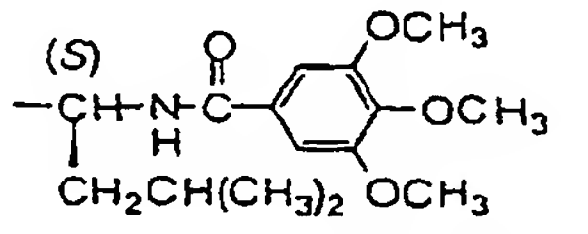
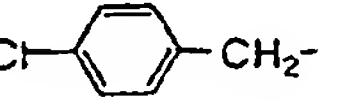
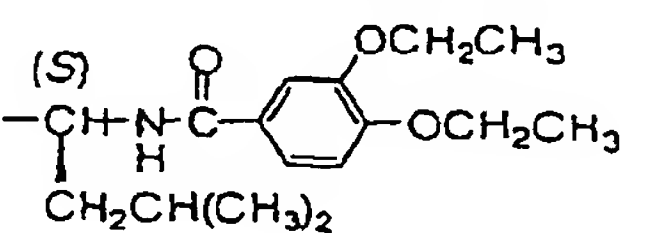
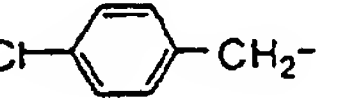
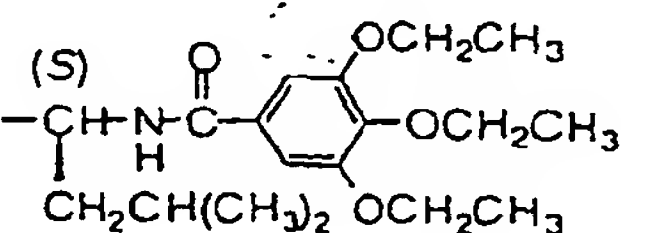
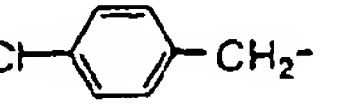
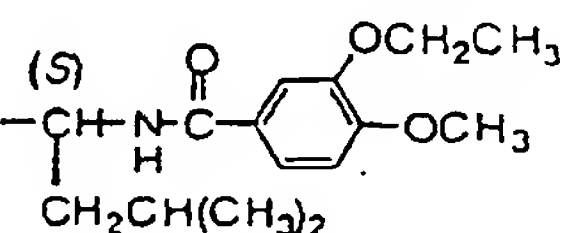
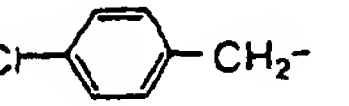
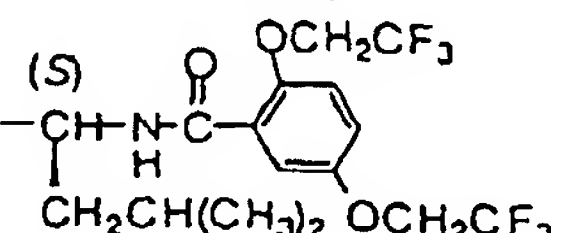
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_l -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1046		2	2	1	-	H	
1047		2	2	1	-	H	
1048		2	2	1	-	H	
1049		2	2	1	-	H	
1050		2	2	1	-	H	
1051		2	2	1	-	H	
1052		2	2	1	-	H	
1053		2	2	1	-	H	
1054		2	2	1	-	H	
1055		2	2	1	-	H	
1056		2	2	1	-	H	

Table 1.97

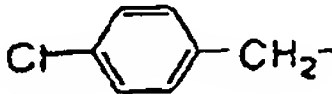
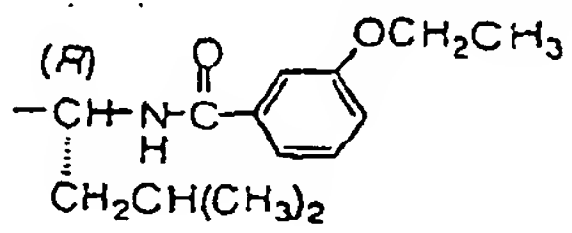
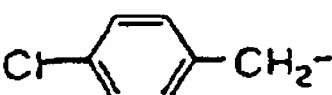
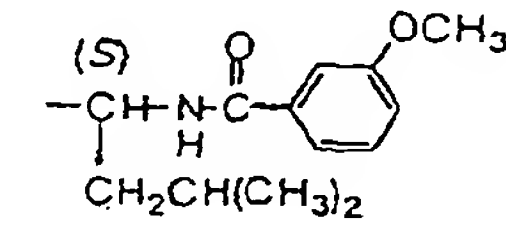
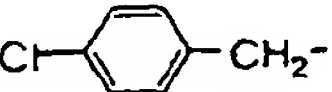
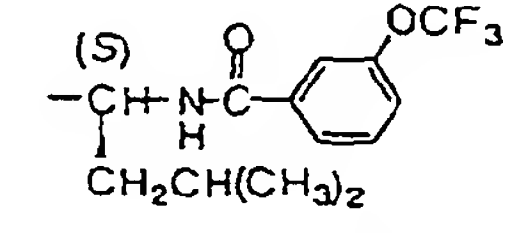
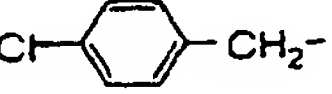
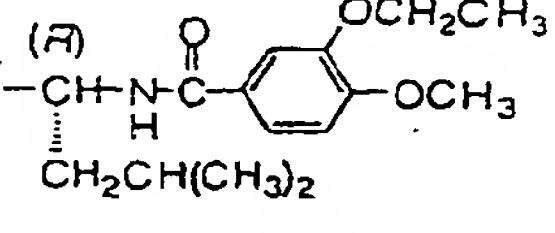

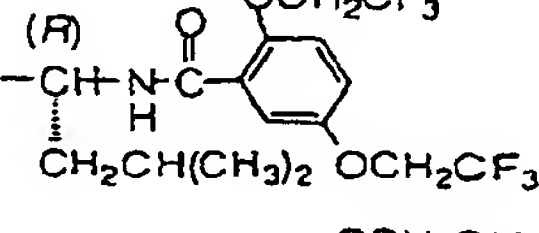
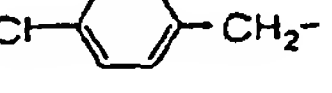
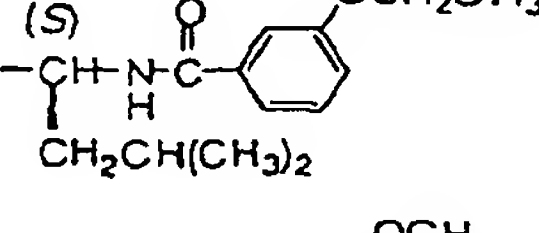
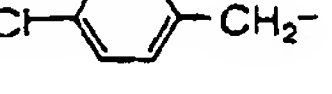
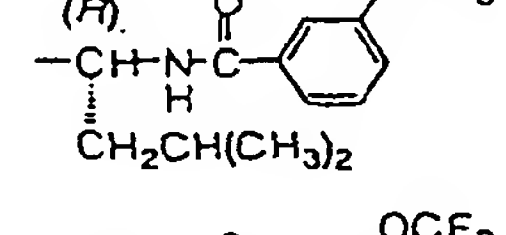

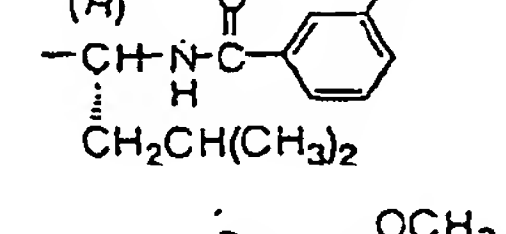

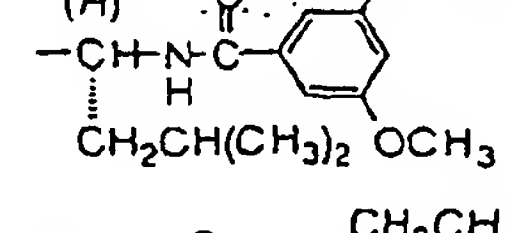
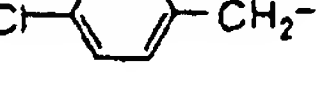
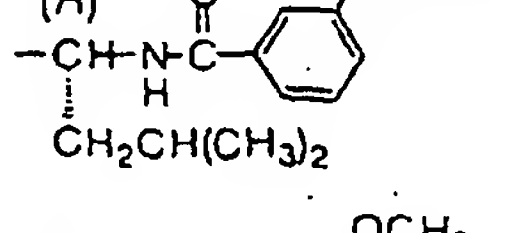

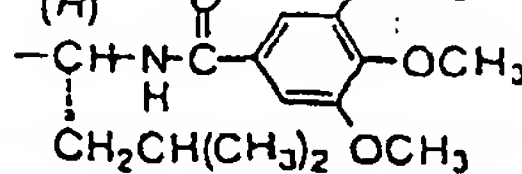
Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (\text{CH}_2)_l \text{---}$	k	m	n	chirality	R^3	$-(\text{CH}_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} \text{---} (\text{CH}_2)_q \text{---} \text{G---} R^6$
1057		2	2	1	-	H	
1058		2	2	1	-	H	
1059		2	2	1	-	H	
1060		2	2	1	-	H	
1061		2	2	1	-	H	
1062		2	2	1	-	H	
1063		2	2	1	-	H	
1064		2	2	1	-	H	
1065		2	2	1	-	H	
1066		2	2	1	-	H	
1067		2	2	1	-	H	

Table 1.98


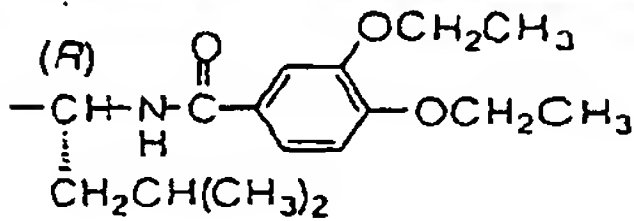
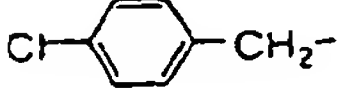
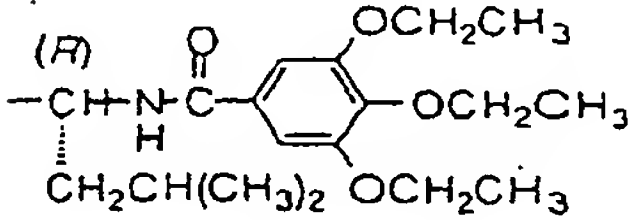
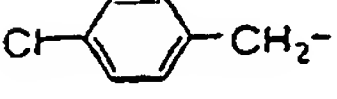
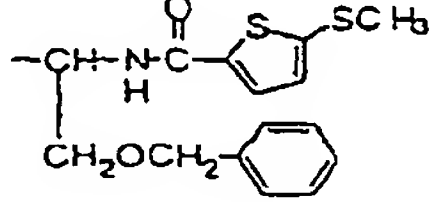
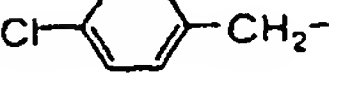
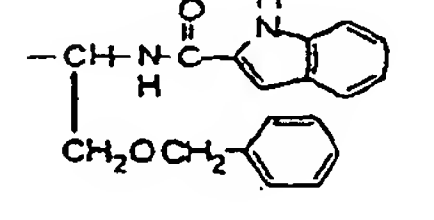
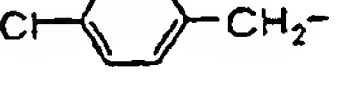
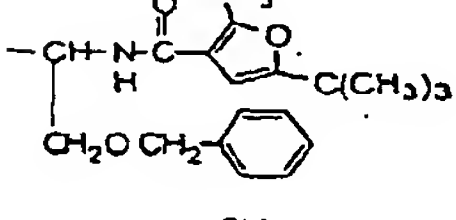

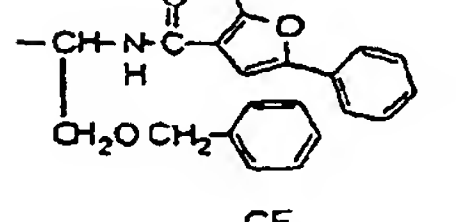

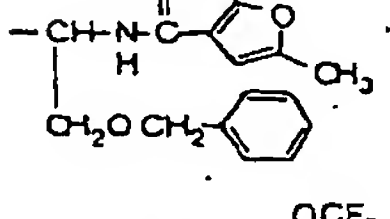

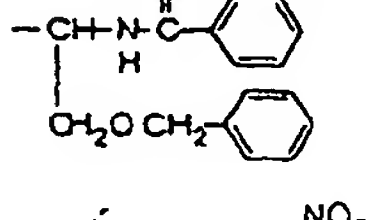

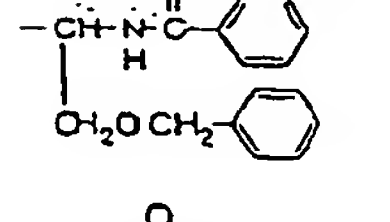

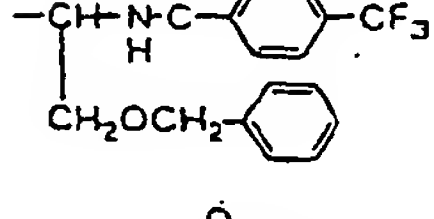
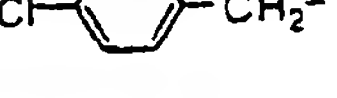
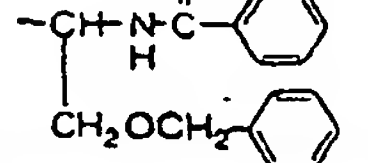
5	Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ R^2 \end{matrix} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
10	1068		2	2	1	-	H	
15	1069		2	2	1	-	H	
20	1070		2	2	1	-	H	
25	1071		2	2	1	-	H	
30	1072		2	2	1	-	H	
35	1073		2	2	1	-	H	
40	1074		2	2	1	-	H	
45	1075		2	2	1	-	H	
50	1076		2	2	1	-	H	
55	1077		2	2	1	-	H	
	1078		2	2	1	-	H	

Table 1.9 9

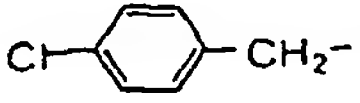
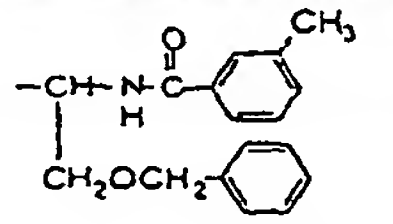
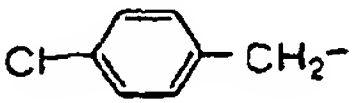
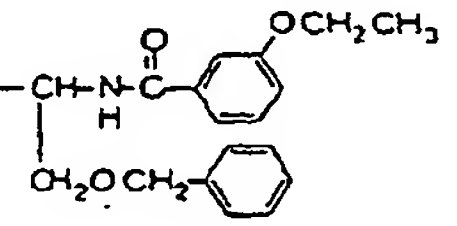
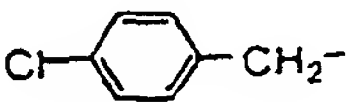
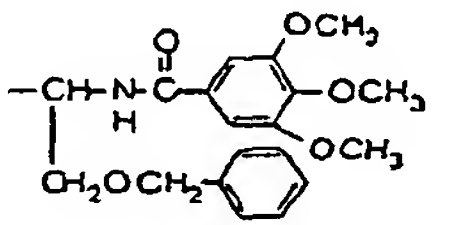
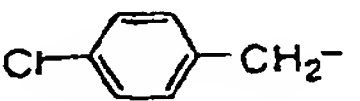
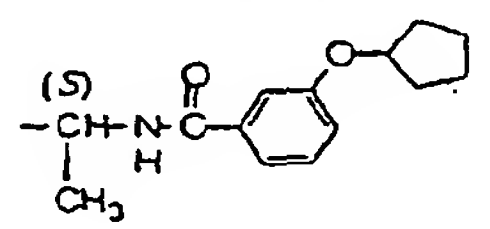
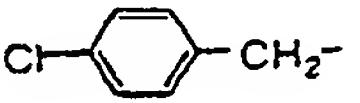
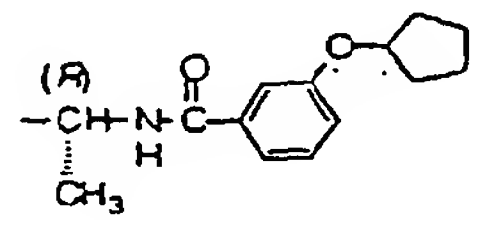
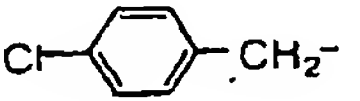
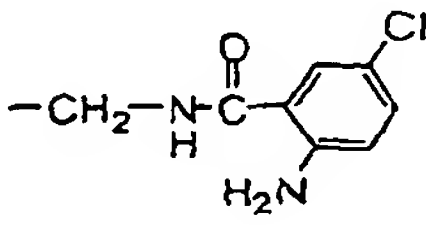
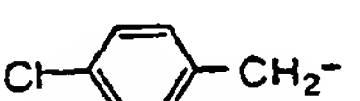
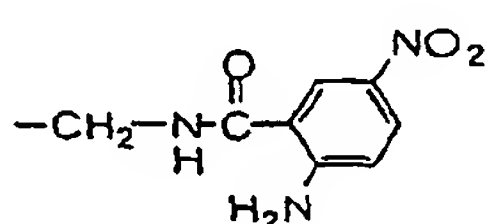
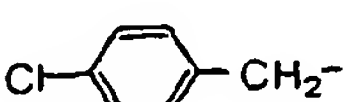
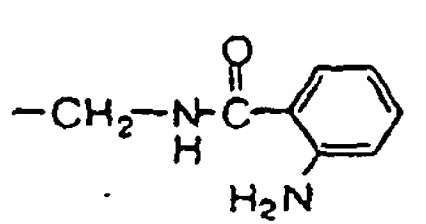

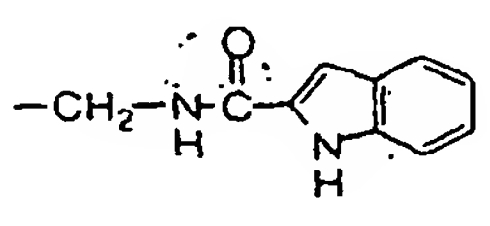
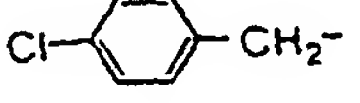
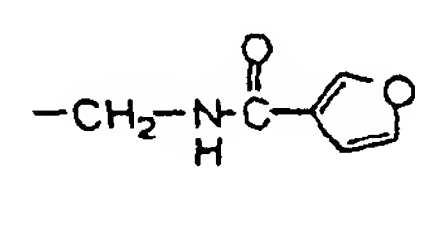
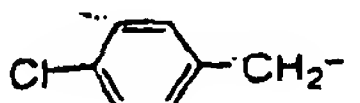
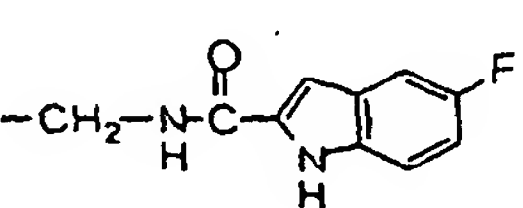
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q G-R^6$
1079		2	2	1	-	H	
1080		2	2	1	-	H	
1081		2	2	1	-	H	
1082		2	2	1	-	H	
1083		2	2	1	-	H	
1084		1	2	0	R	H	
1085		1	2	0	R	H	
1086		1	2	0	R	H	
1087		1	2	0	R	H	
1088		1	2	0	R	H	
1089		1	2	0	R	H	

Table 1.100

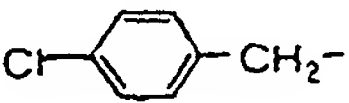
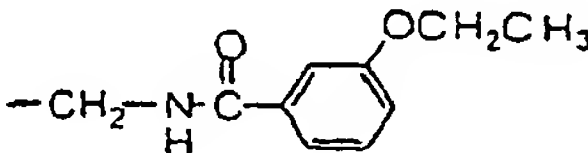
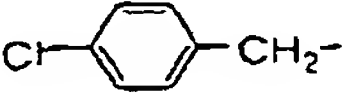
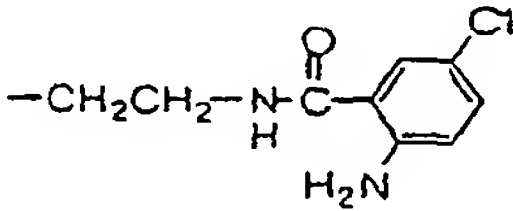
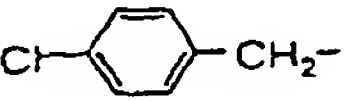
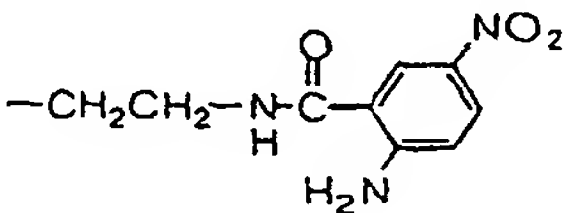
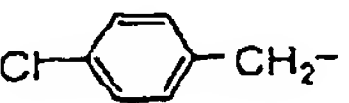
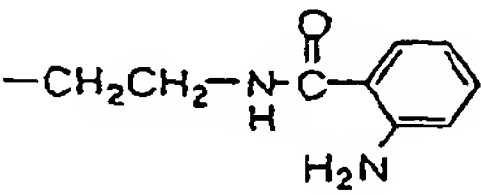
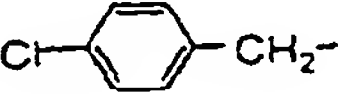
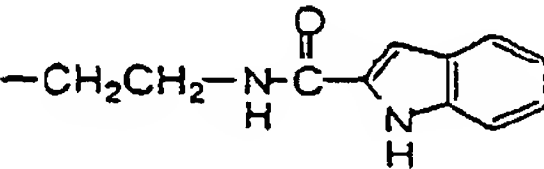
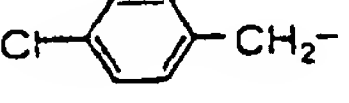
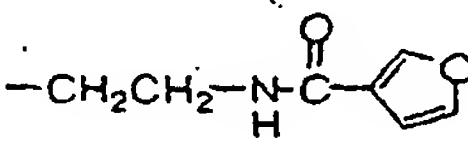
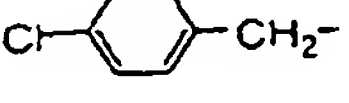
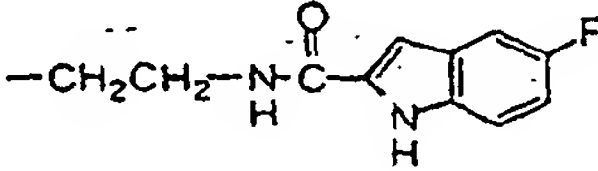
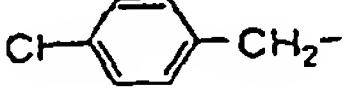
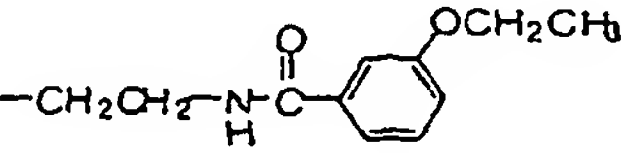
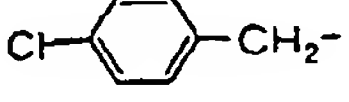
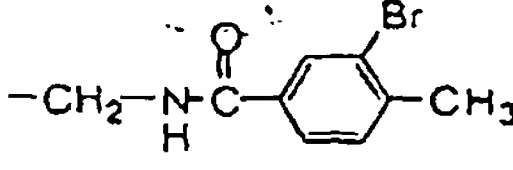
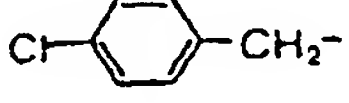
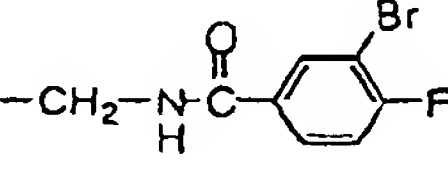
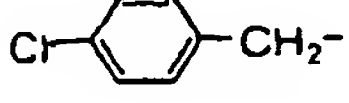
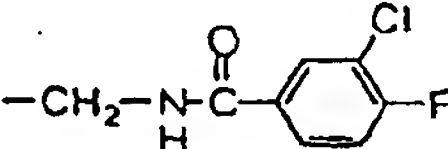
Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ (CH_2)_k \\ \diagdown \\ R^2 \end{matrix}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
1090		1	2	0	R	H	
1091		1	2	0	R	H	
1092		1	2	0	R	H	
1093		1	2	0	R	H	
1094		1	2	0	R	H	
1095		1	2	0	R	H	
1096		1	2	0	R	H	
1097		1	2	0	R	H	
1098		1	2	0	R	H	
1099		1	2	0	R	H	
1100		1	2	0	R	H	

Table 1.101

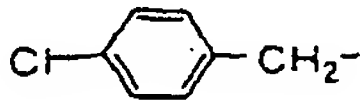
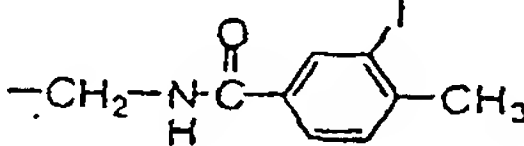
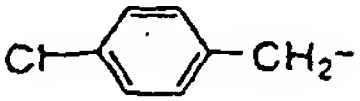
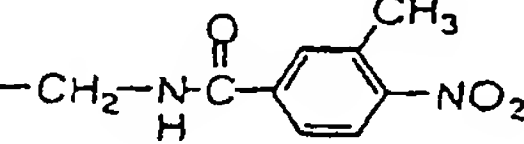

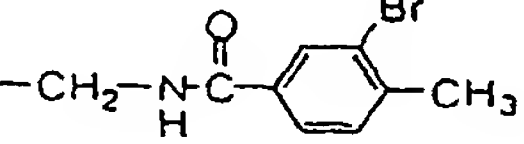
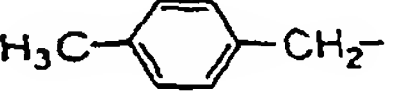
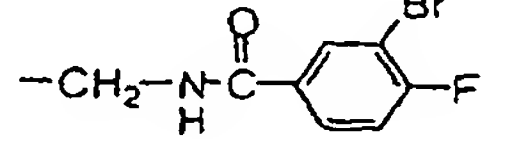
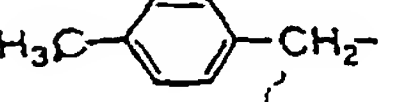
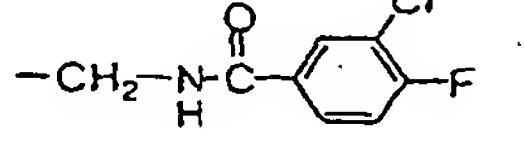
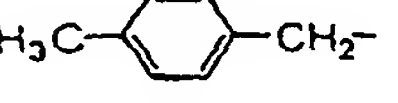
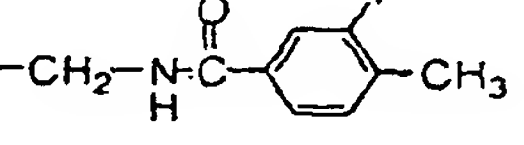
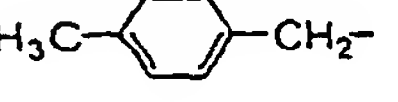
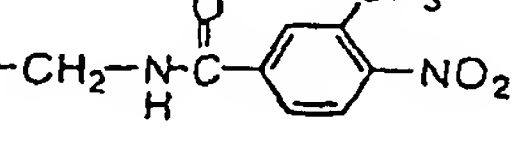
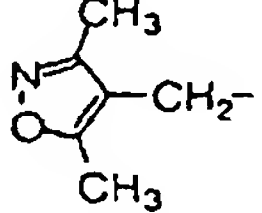
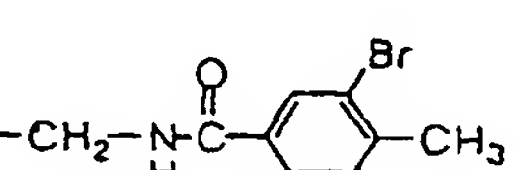
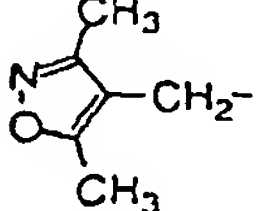
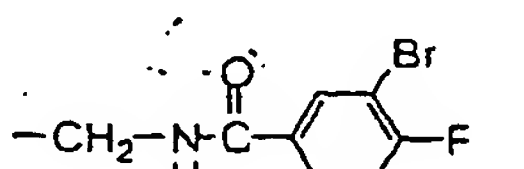
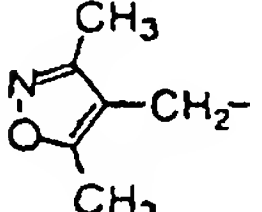
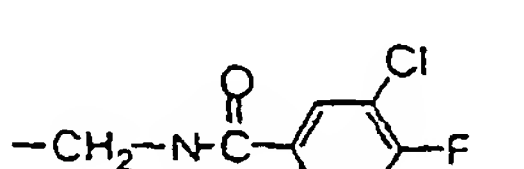
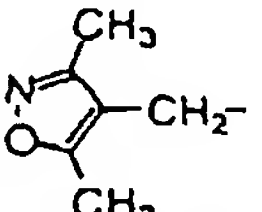
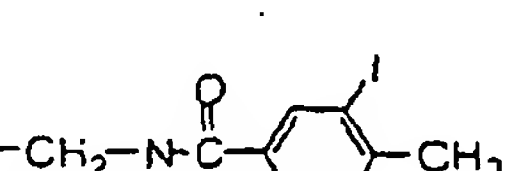
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_k- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p-\overset{\overset{R^4}{ }}{\underset{\underset{R^5}{ }}{C}}-(CH_2)_q-G-R^6$
1101		1	2	0	R	H	
1102		1	2	0	R	H	
1103		1	2	0	R	H	
1104		1	2	0	R	H	
1105		1	2	0	R	H	
1106		1	2	0	R	H	
1107		1	2	0	R	H	
1108		1	2	0	R	H	
1109		1	2	0	R	H	
1110		1	2	0	R	H	
1111		1	2	0	R	H	

Table 1.102

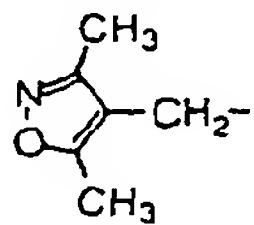
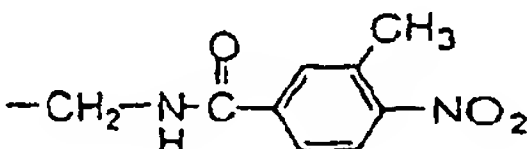
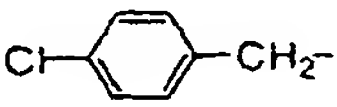
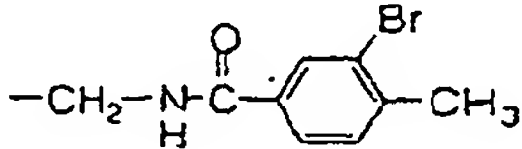
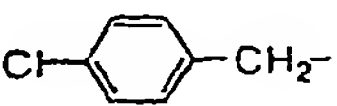
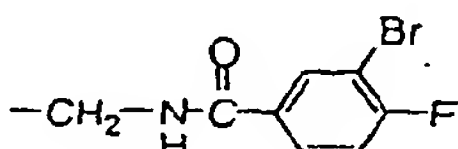
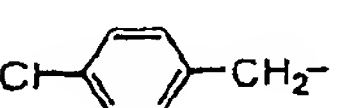
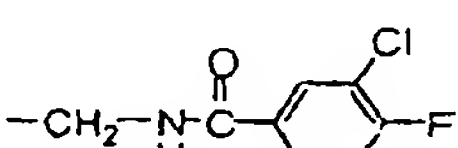
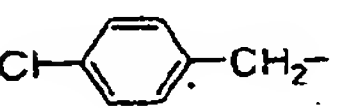
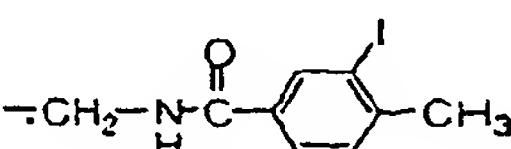
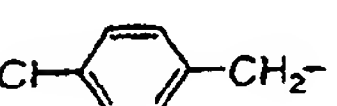
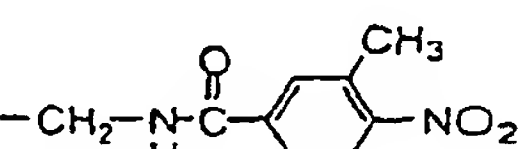
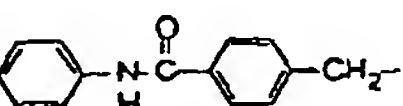
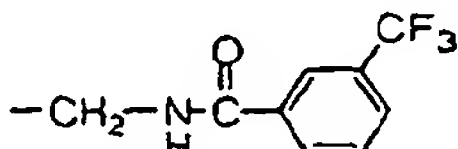

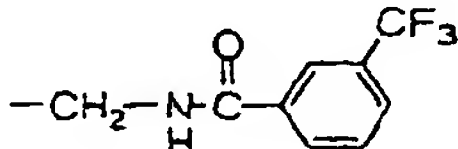
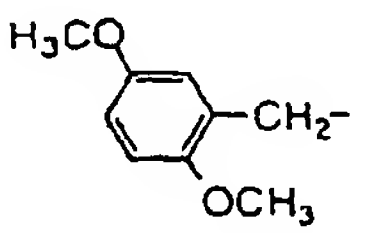
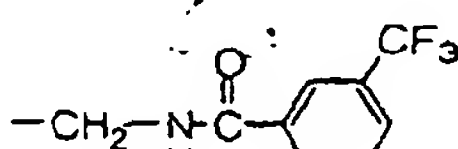
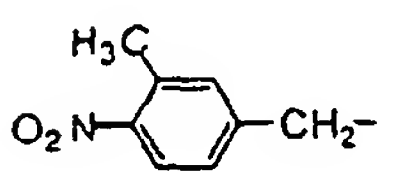
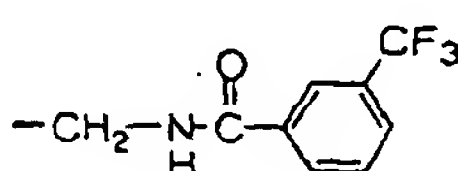
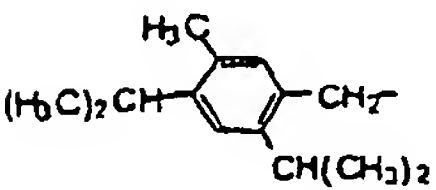
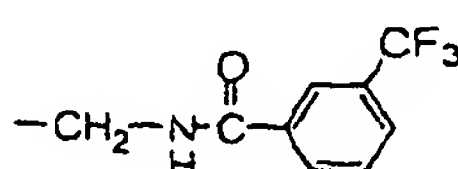
Compd. No.	$\begin{array}{c} R^1 \\ \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1112		1	2	0	R	H	
1113		2	2	1	-	H	
1114		2	2	1	-	H	
1115		2	2	1	-	H	
1116		2	2	1	-	H	
1117		2	2	1	-	H	
1118		1	2	0	R	H	
1119		1	2	0	R	H	
1120		1	2	0	R	H	
1121		1	2	0	R	H	
1122		1	2	0	R	H	

Table 1.103

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1123		1	2	0	R	H	
1124		1	2	0	R	H	
1125		2	2	1	-	H	
1126		2	2	1	-	H	
1127		2	2	1	-	H	
1128		2	2	1	-	H	
1129		2	2	1	-	H	
1130		2	2	1	-	H	
1131		2	2	1	-	H	
1132		2	2	1	-	H	
1133		1	2	0	R	H	

Table 1.104

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_i$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1134		1	2	0	R	H	
1135		1	2	0	R	H	
1136		1	2	0	R	H	
1137		1	2	0	R	H	
1138		1	2	0	R	H	
1139		1	2	0	R	H	
1140		1	2	0	R	H	
1141		1	2	0	R	H	
1142		1	2	0	R	H	
1143		1	2	0	R	H	
1144		1	2	0	R	H	

Table 1.105

5	Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
10	1145		1	2	0	R	H	
15	1146		1	2	0	R	H	
20	1147		1	2	0	R	H	
25	1148		1	2	0	R	H	
30	1149		1	2	0	R	H	
35	1150		1	2	0	R	H	
40	1151		1	2	0	R	H	
45	1152		1	2	0	R	H	
50	1153		1	2	0	R	H	
55	1154		1	2	0	R	H	
	1155		1	2	0	R	H	

Table 1.106

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_k \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1156		1	2	0	R	H	
1157		1	2	0	R	H	
1158		1	2	0	R	H	
1159		1	2	0	R	H	
1160		1	2	0	R	H	
1161		1	2	0	R	H	
1162		1	2	0	R	H	
1163		1	2	0	R	H	
1164		1	2	0	R	H	
1165		1	2	0	R	H	
1166		1	2	0	R	H	

Table 1.107

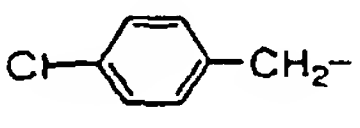
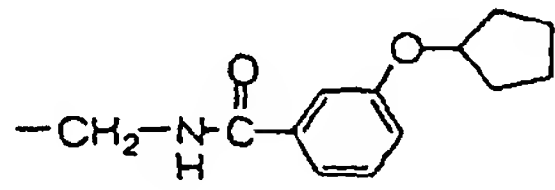
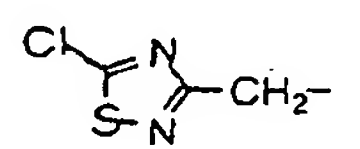
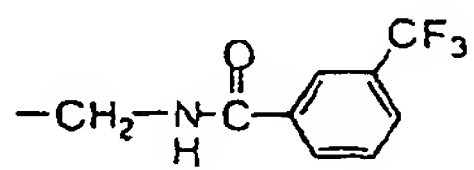
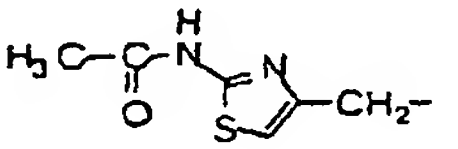
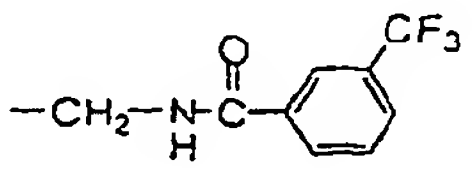
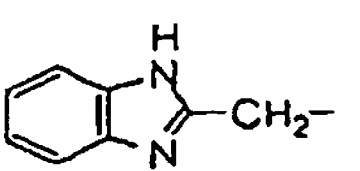
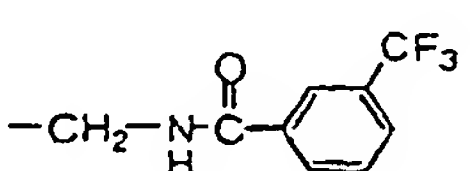
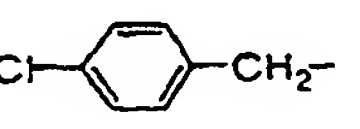
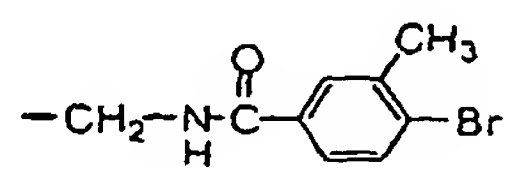
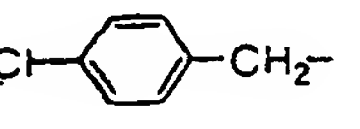
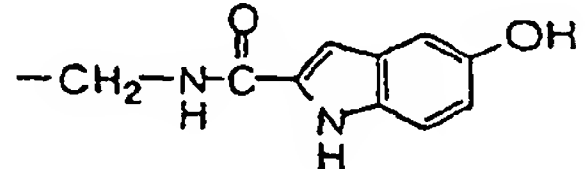
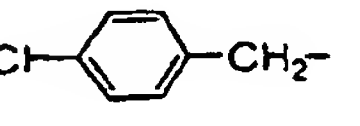
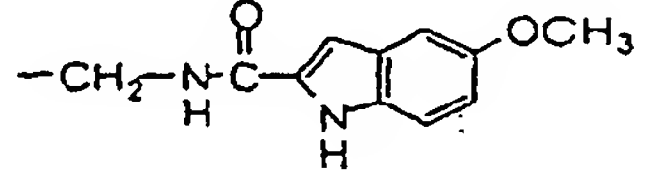
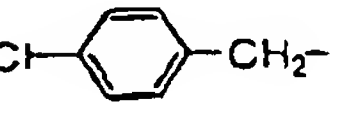
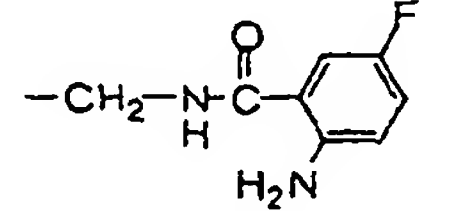

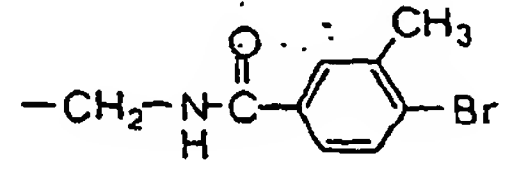
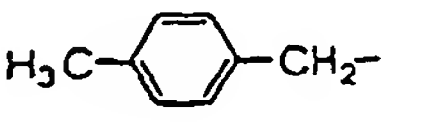
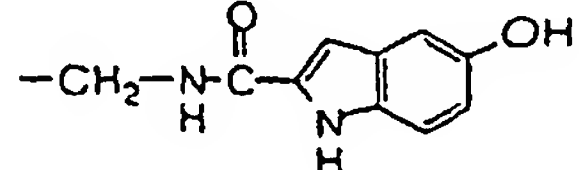
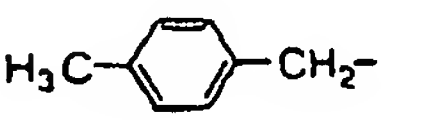
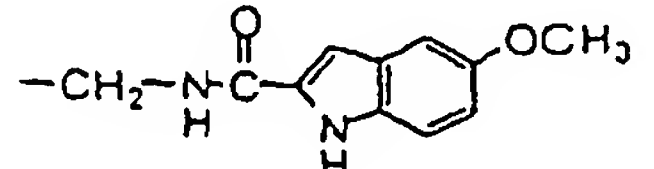
5 Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
10 1167		2	2	1	-	H	
15 1168		1	2	0	R	H	
20 1169		1	2	0	R	H	
25 1170		1	2	0	R	H	
30 1171		1	2	0	R	H	
35 1172		1	2	0	R	H	
40 1173		1	2	0	R	H	
45 1174		1	2	0	R	H	
50 1175		1	2	0	R	H	
55 1176		1	2	0	R	H	
1177		1	2	0	R	H	

Table 1.108

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_i \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1178		1	2	0	R	H	
1179		1	2	0	R	H	
1180		1	2	0	R	H	
1181		1	2	0	R	H	
1182		1	2	0	R	H	
1183		1	2	0	R	H	
1184		1	2	0	R	H	
1185		1	2	0	R	H	
1186		1	2	0	R	H	
1187		2	2	1	-	H	
1188		2	2	1	-	H	

Table 1.109

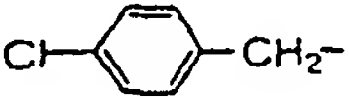
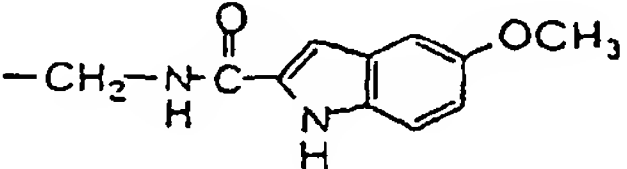

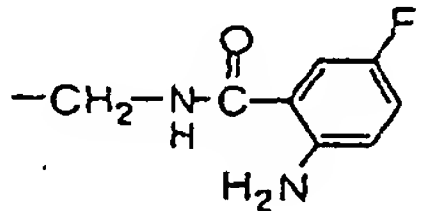
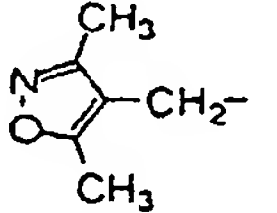
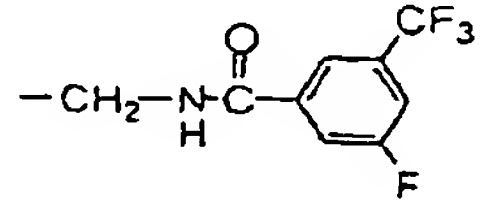
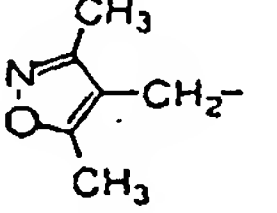
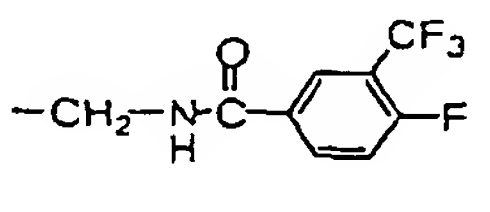
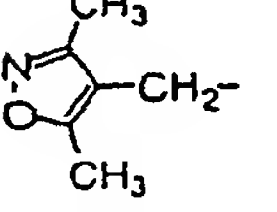
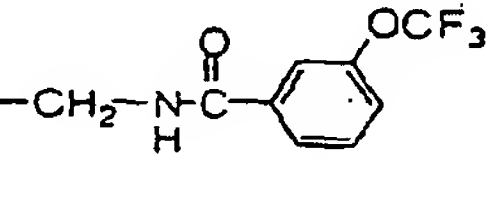
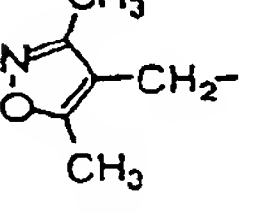
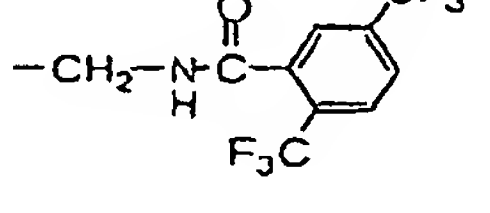
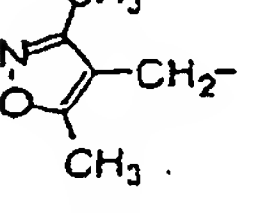
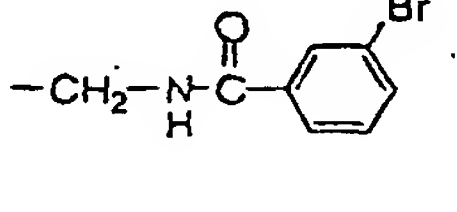
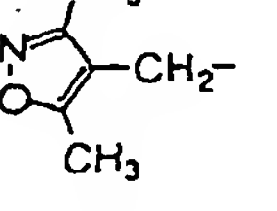
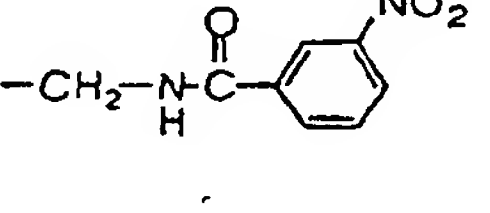
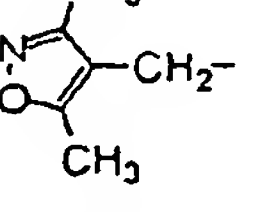
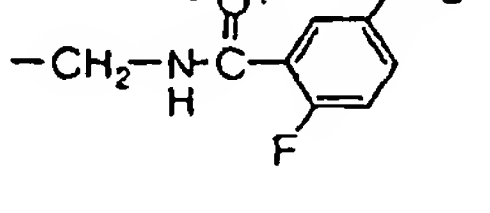
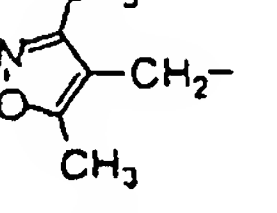
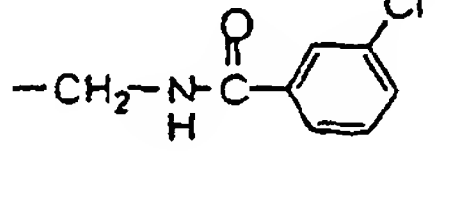
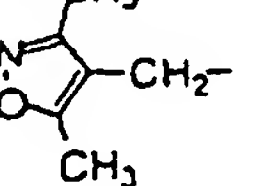
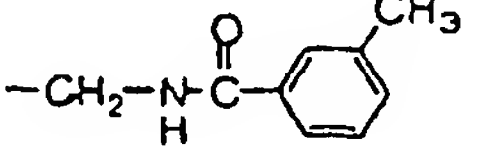
5 Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
10 1189		2	2	1	-	H	
15 1190		2	2	1	-	H	
20 1191		1	2	0	R	H	
25 1192		1	2	0	R	H	
30 1193		1	2	0	R	H	
35 1194		1	2	0	R	H	
40 1195		1	2	0	R	H	
45 1196		1	2	0	R	H	
50 1197		1	2	0	R	H	
55 1198		1	2	0	R	H	
1199		1	2	0	R	H	

Table 1.110

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1200		1	2	0	R	H	
1201		1	2	0	R	H	
1202		1	2	0	R	H	
1203		1	2	0	R	H	
1204		1	2	0	R	H	
1205		1	2	0	R	H	
1206		1	2	0	R	H	
1207		1	2	0	R	H	
1208		1	2	0	R	H	
1209		1	2	0	R	H	
1210		1	2	0	R	H	

Table 1.111

Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (CH_2)_j \text{---}$	k	m	n	chirality	R^3	$-(CH_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} \text{---} (CH_2)_q \text{---} G \text{---} R^6$
1211	$H_3C \text{---} \text{C}_6\text{H}_4 \text{---} CH_2 \text{---}$	1	2	0	R	H	$-CH_2 \text{---} NH \text{---} C(=O) \text{---} \text{C}_6\text{H}_3(F)_2$
1212	$H_3C \text{---} \text{C}_6\text{H}_4 \text{---} CH_2 \text{---}$	1	2	0	R	H	$-CH_2 \text{---} NH \text{---} C(=O) \text{---} \text{C}_6\text{H}_3(F)(CF_3)$
1213	$Cl \text{---} \text{C}_6\text{H}_4 \text{---} CH_2 \text{---}$	2	2	1	-	H	$-CH_2 \text{---} NH \text{---} C(=O) \text{---} \text{C}_6\text{H}_2(F)(CF_3)_2$
1214	$Cl \text{---} \text{C}_6\text{H}_4 \text{---} CH_2 \text{---}$	2	2	1	-	H	$-CH_2 \text{---} NH \text{---} C(=O) \text{---} \text{C}_6\text{H}_2(F)(CF_3)$
1215	$Cl \text{---} \text{C}_6\text{H}_4 \text{---} CH_2 \text{---}$	2	2	1	-	H	$-CH_2 \text{---} NH \text{---} C(=O) \text{---} \text{C}_6\text{H}_2(Cl)_2$
1216	$Cl \text{---} \text{C}_6\text{H}_4 \text{---} CH_2 \text{---}$	2	2	1	-	H	$-CH_2 \text{---} NH \text{---} C(=O) \text{---} \text{C}_6\text{H}_3(F)_2$
1217	$Cl \text{---} \text{C}_6\text{H}_4 \text{---} CH_2 \text{---}$	1	2	0	R	H	$-CH_2 \text{---} NH \text{---} C(=O) \text{---} \text{C}_6\text{H}_3(Cl)(CF_3)$
1218	$Cl \text{---} \text{C}_6\text{H}_4 \text{---} CH_2 \text{---}$	1	2	0	R	H	$-CH_2 \text{---} NH \text{---} C(=O) \text{---} \text{C}_6\text{H}_3(F)(CH_3)$
1219	$Cl \text{---} \text{C}_6\text{H}_4 \text{---} CH_2 \text{---}$	1	2	0	R	H	$-CH_2 \text{---} NH \text{---} C(=O) \text{---} \text{C}_6\text{H}_3(Cl)(CH_3)$
1220	$Cl \text{---} \text{C}_6\text{H}_4 \text{---} CH_2 \text{---}$	1	2	0	R	H	$-CH_2 \text{---} NH \text{---} C(=O) \text{---} \text{C}_6\text{H}_3(I)(NH_2)$
1221	$Cl \text{---} \text{C}_6\text{H}_4 \text{---} CH_2 \text{---}$	1	2	0	R	H	$-CH_2 \text{---} NH \text{---} C(=O) \text{---} \text{C}_6\text{H}_3(F)_2(NH_2)$

Table 1.112

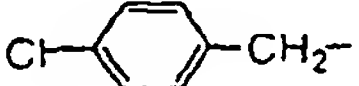
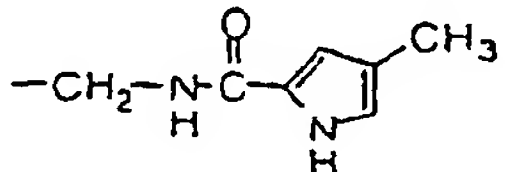

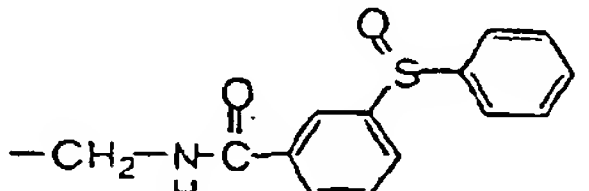
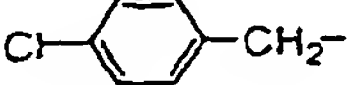
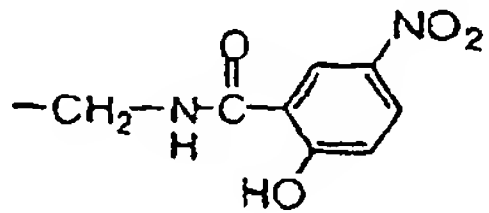

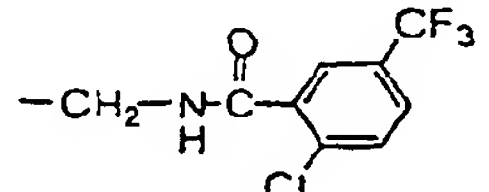

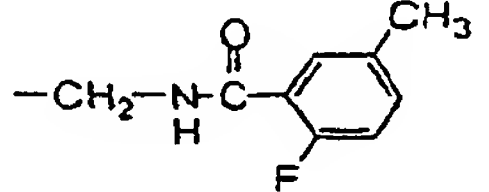

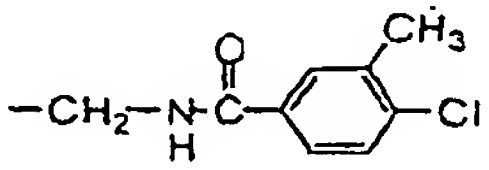

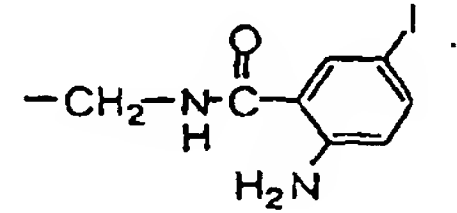
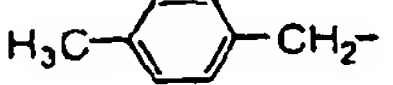
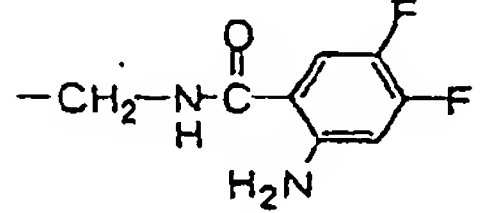
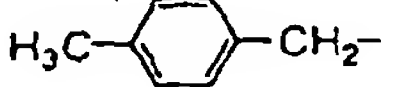
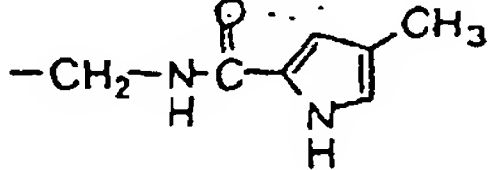

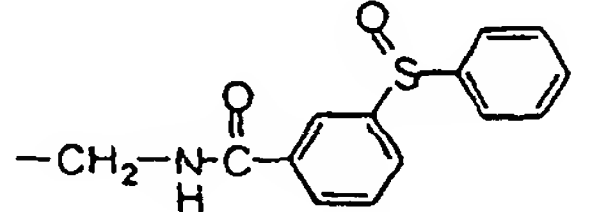

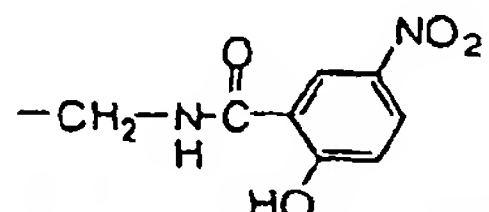
Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (CH_2)_l \text{---}$	k	m	n	chirality	R^3	$-(CH_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} \text{---} (CH_2)_q \text{---} G \text{---} R^6$
1222		1	2	0	R	H	
1223		1	2	0	R	H	
1224		1	2	0	R	H	
1225		1	2	0	R	H	
1226		1	2	0	R	H	
1227		1	2	0	R	H	
1228		1	2	0	R	H	
1229		1	2	0	R	H	
1230		1	2	0	R	H	
1231		1	2	0	R	H	
1232		1	2	0	R	H	

Table 1.113

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ (CH_2)_q \\ \\ R^5 \end{array} G-R^6$
1233		1	2	0	R	H	
1234		1	2	0	R	H	
1235		1	2	0	R	H	
1236		1	2	0	R	H	
1237		1	2	0	R	H	
1238		1	2	0	R	H	
1239		1	2	0	R	H	
1240		1	2	0	R	H	
1241		2	2	1	-	H	
1242		2	2	1	-	H	
1243		2	2	1	-	H	

Table 1.114

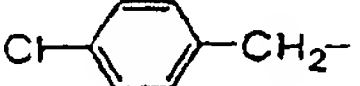
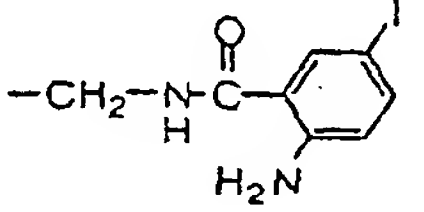
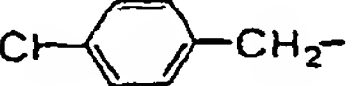
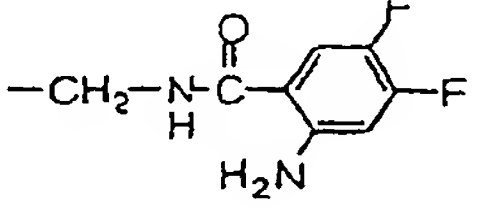

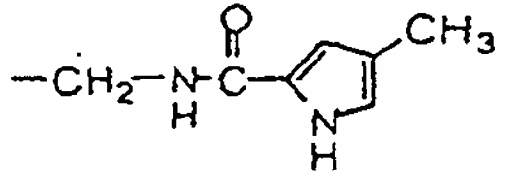
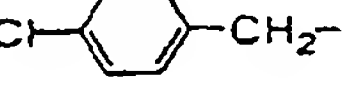
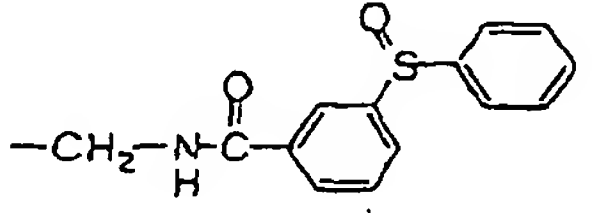
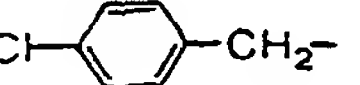
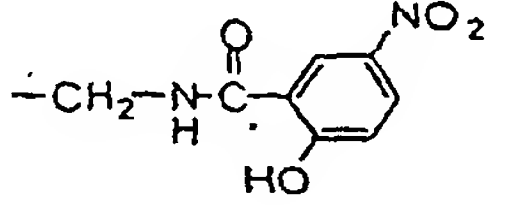
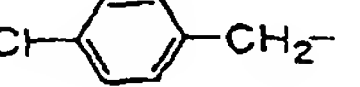
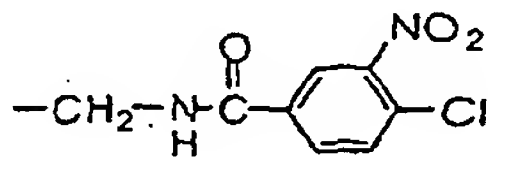
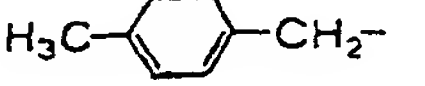
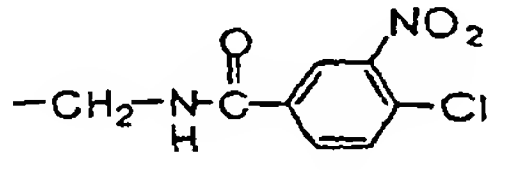
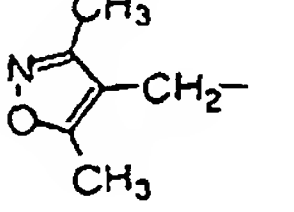
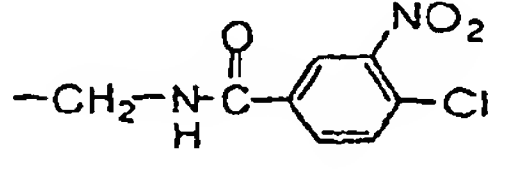

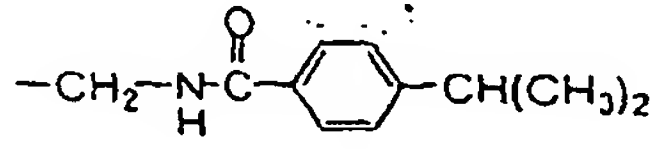

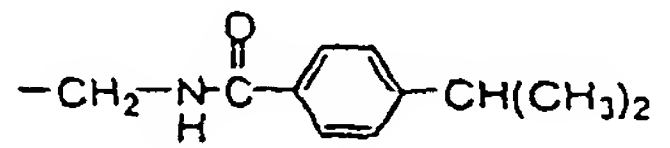
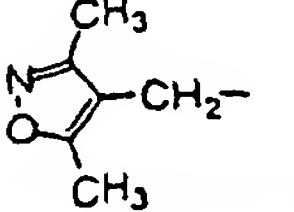
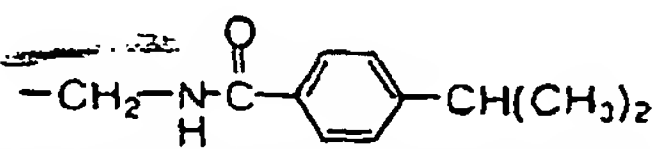
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_i -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1244		2	2	1	-	H	
1245		2	2	1	-	H	
1246		2	2	1	-	H	
1247		2	2	1	-	H	
1248		2	2	1	-	H	
1249		1	2	0	R	H	
1250		1	2	0	R	H	
1251		1	2	0	R	H	
1252		1	2	0	R	H	
1253		1	2	0	R	H	
1254		1	2	0	R	H	

Table 1.115

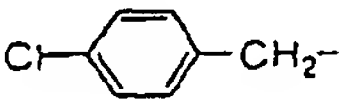
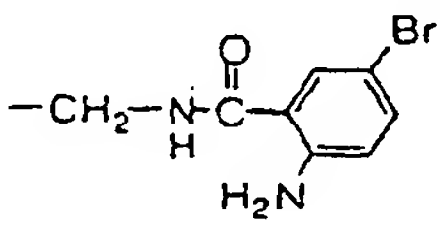
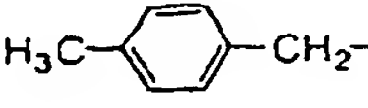
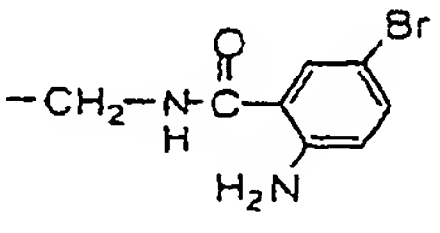
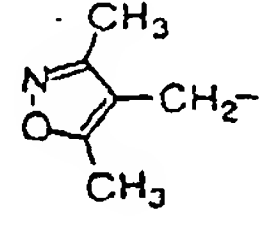
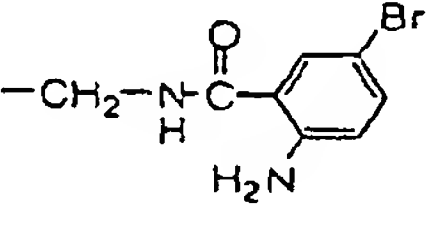
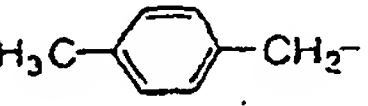
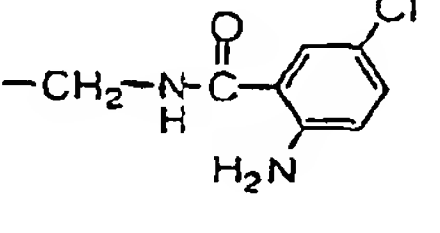
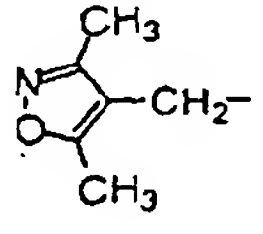
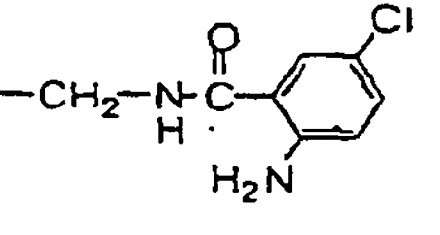
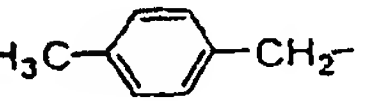
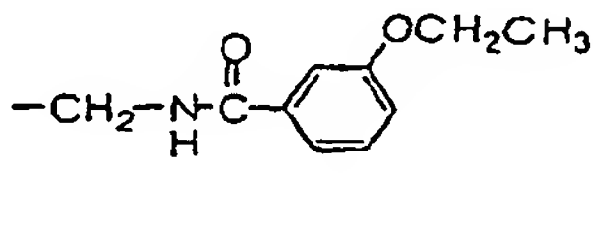
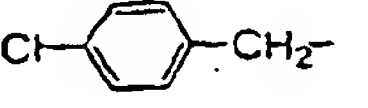
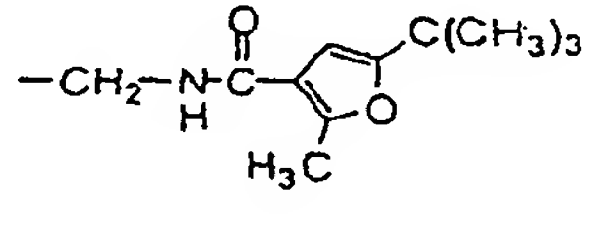
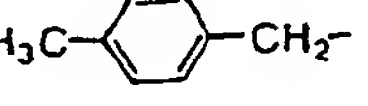
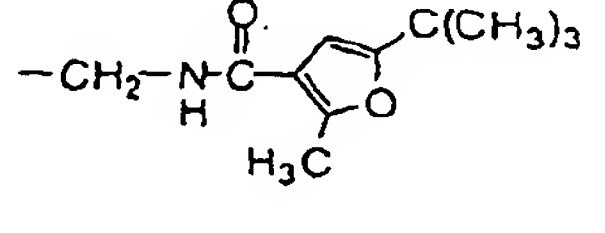
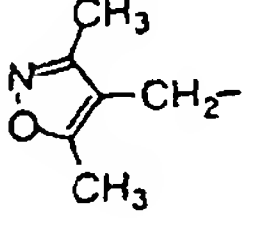
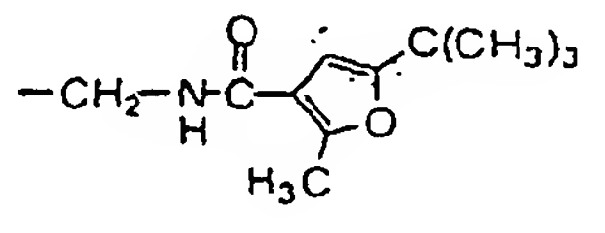
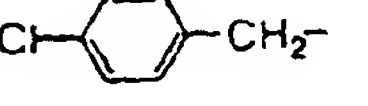
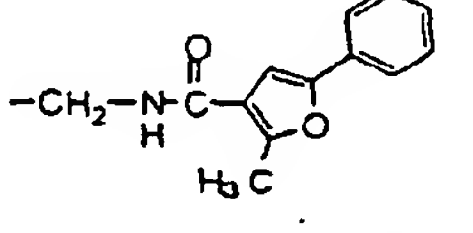
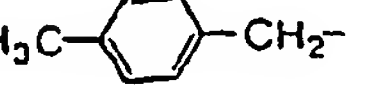
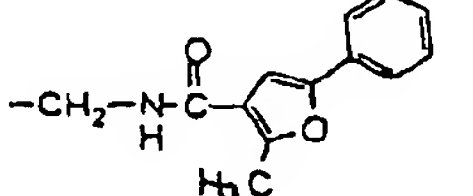
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_k \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ (CH_2)_q \\ \\ R^5 \end{array} G-R^6$
1255		1	2	0	R	H	
1256		1	2	0	R	H	
1257		1	2	0	R	H	
1258		1	2	0	R	H	
1259		1	2	0	R	H	
1260		1	2	0	R	H	
1261		1	2	0	R	H	
1262		1	2	0	R	H	
1263		1	2	0	R	H	
1264		1	2	0	R	H	
1265		1	2	0	R	H	

Table 1.116

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1266		1	2	0	R	H	
1267		1	2	0	R	H	
1268		1	2	0	R	H	
1269		1	2	0	R	H	
1270		1	2	0	R	H	
1271		1	2	0	R	H	
1272		1	2	0	R	H	
1273		1	2	0	R	H	
1274		1	2	0	R	H	
1275		1	2	0	R	H	
1276		1	2	0	R	H	

Table 1.117

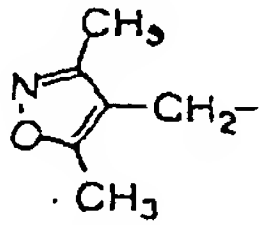
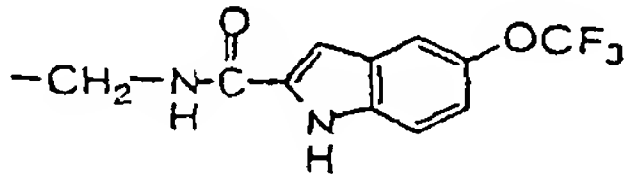
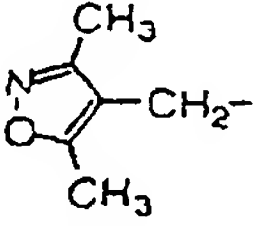
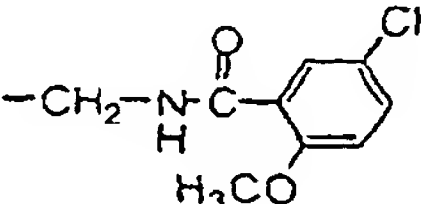
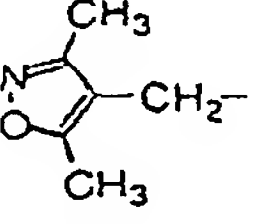
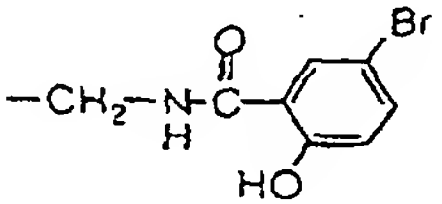
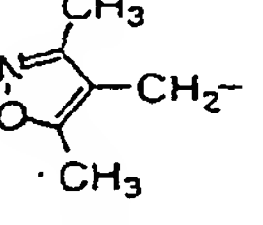
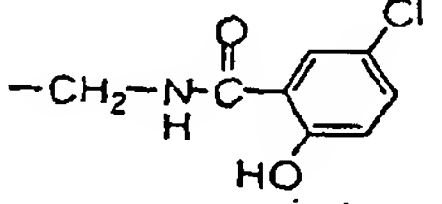
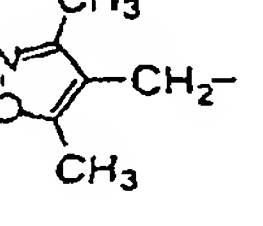
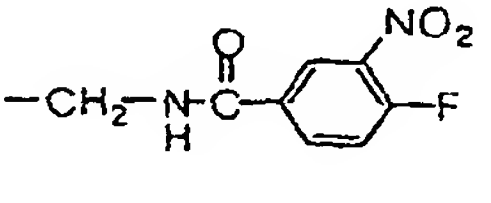
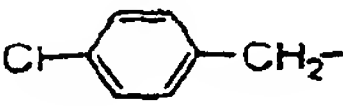
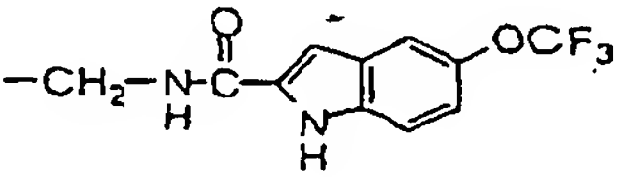
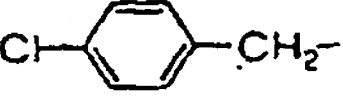
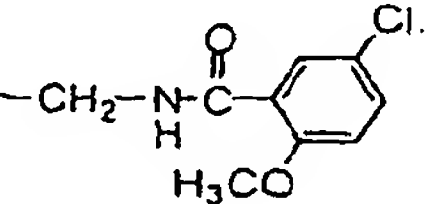
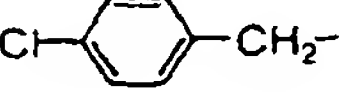
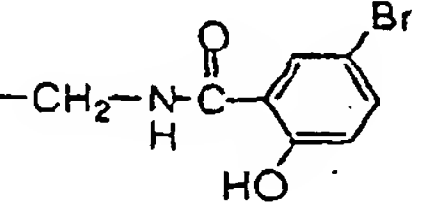
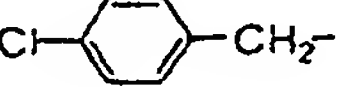
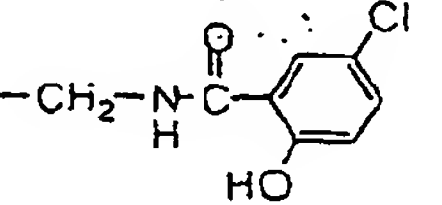
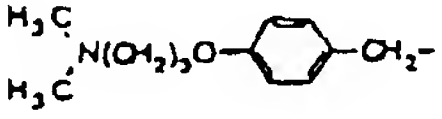
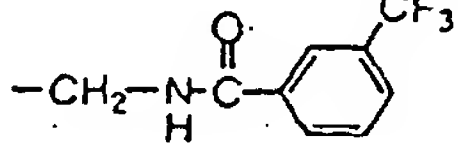
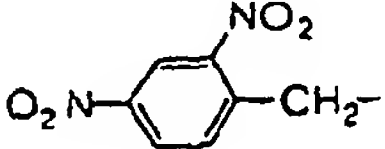
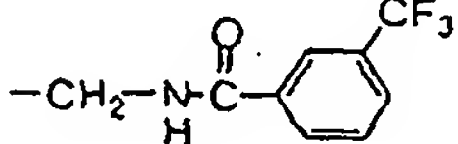
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_i -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1277		1	2	0	R	H	
1278		1	2	0	R	H	
1279		1	2	0	R	H	
1280		1	2	0	R	H	
1281		1	2	0	R	H	
1282		2	2	1	-	H	
1283		2	2	1	-	H	
1284		2	2	1	-	H	
1285		2	2	1	-	H	
1286		1	2	0	R	H	
1287		1	2	0	R	H	

Table 1.118

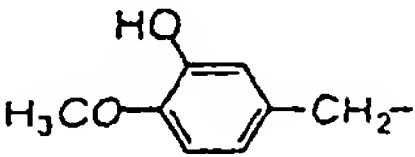
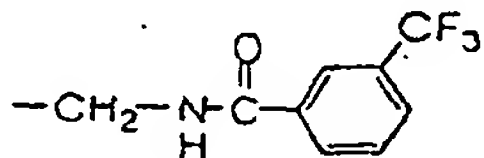
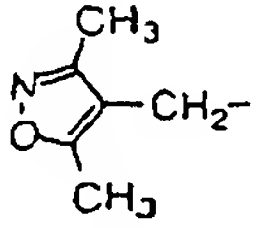
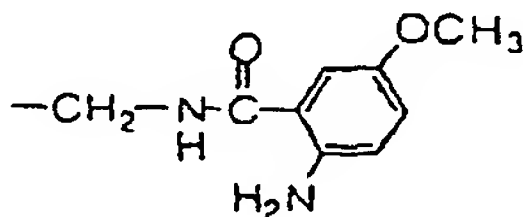
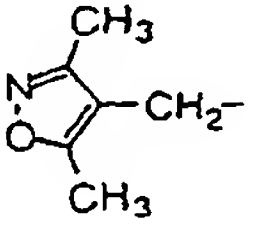
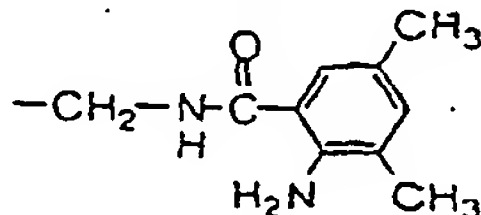

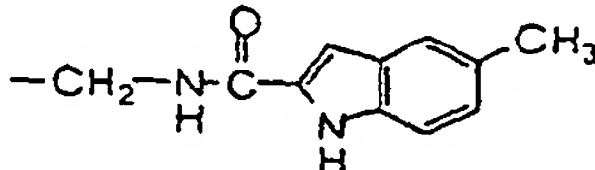

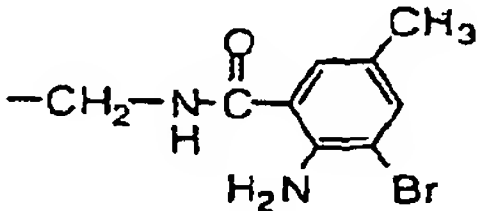

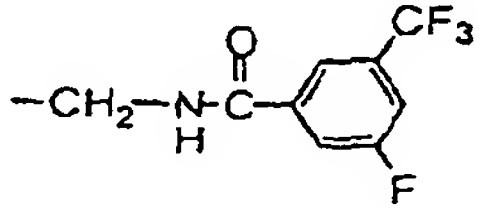
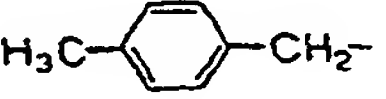
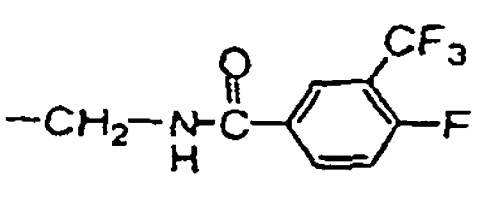
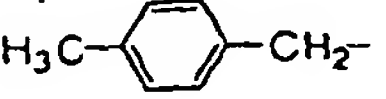
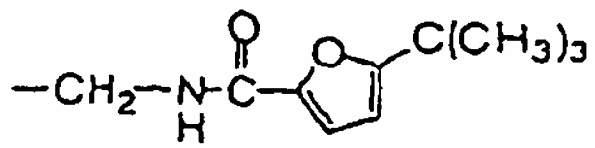
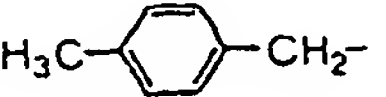
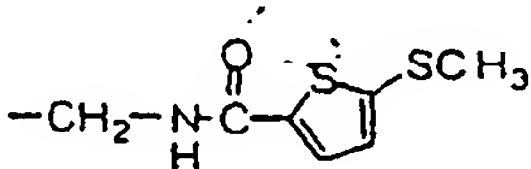
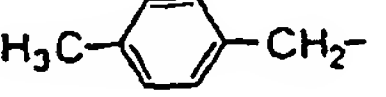
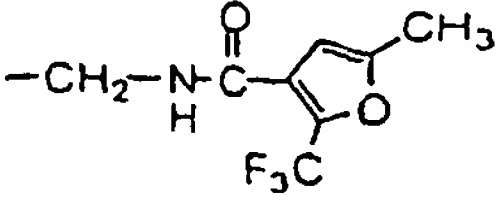
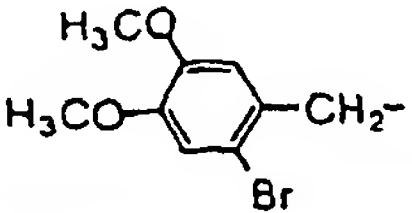
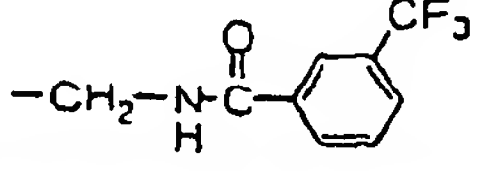
5 Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
10 1288		1	2	0	R	H	
15 1289		1	2	0	R	H	
20 1290		1	2	0	R	H	
25 1291		1	2	0	R	H	
30 1292		1	2	0	R	H	
35 1293		1	2	0	R	H	
40 1294		1	2	0	R	H	
45 1295		1	2	0	R	H	
50 1296		1	2	0	R	H	
55 1297		1	2	0	R	H	
1298		1	2	0	R	H	

Table 1.119

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1299		1	2	0	R	H	
1300		1	2	0	R	H	
1301		1	2	0	R	H	
1302		1	2	0	R	H	
1303		1	2	0	R	H	
1304		1	2	0	R	H	
1305		1	2	0	R	H	
1306		1	2	0	R	H	
1307		1	2	0	R	H	
1308		1	2	0	R	H	
1309		1	2	0	R	H	

Table 1.120

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1310		1	2	0	R	H	
1311		1	2	0	R	H	
1312		1	2	0	R	H	
1313		1	2	0	R	H	
1314		1	2	0	R	H	
1315		1	2	0	R	H	
1316		1	2	0	R	H	
1317		1	2	0	R	H	
1318		1	2	0	R	H	
1319		1	2	0	R	H	
1320		1	2	0	R	H	

Table 1.121

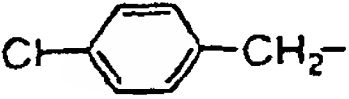
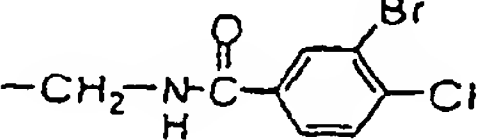
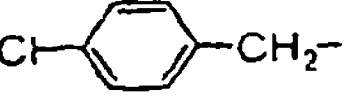
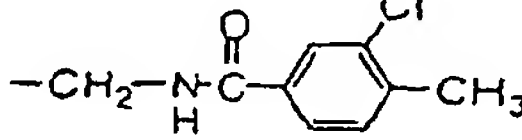
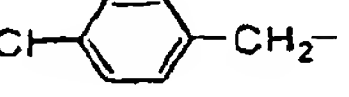
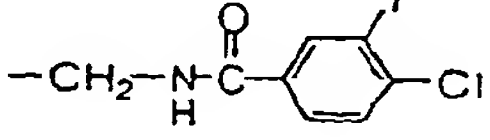
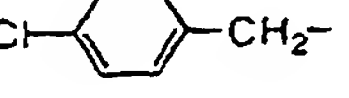
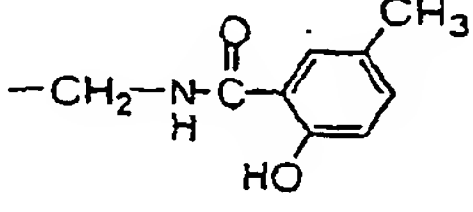
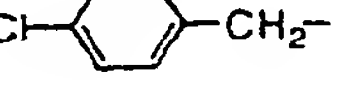
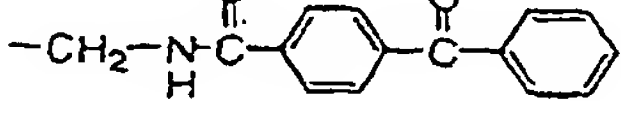
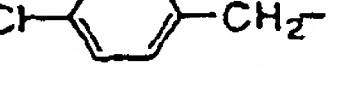
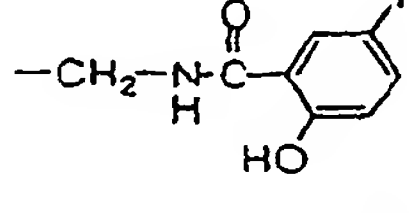
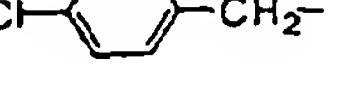
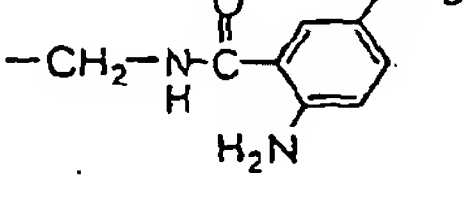
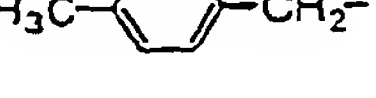
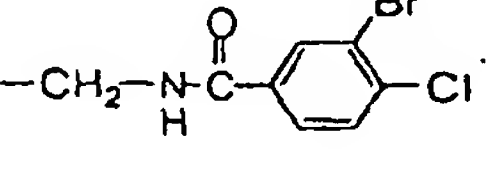
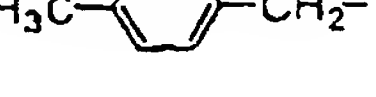
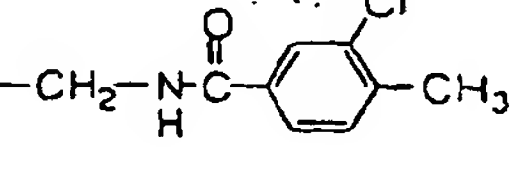
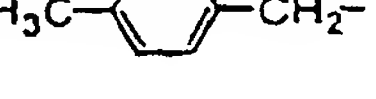
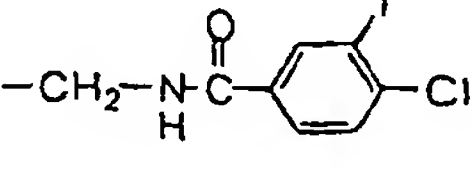
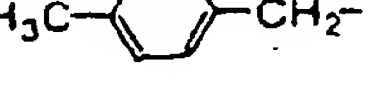
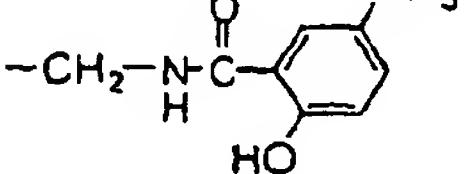
Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (CH_2)_j \text{---}$	k	m	n	chirality	R^3	$-(CH_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} \text{---} (CH_2)_q \text{---} G \text{---} R^6$
1321		1	2	0	R	H	
1322		1	2	0	R	H	
1323		1	2	0	R	H	
1324		1	2	0	R	H	
1325		1	2	0	R	H	
1326		1	2	0	R	H	
1327		1	2	0	R	H	
1328		1	2	0	R	H	
1329		1	2	0	R	H	
1330		1	2	0	R	H	
1331		1	2	0	R	H	

Table 1.122

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1332		1	2	0	R	H	
1333		1	2	0	R	H	
1334		1	2	0	R	H	
1335		1	2	0	R	H	
1336		1	2	0	R	H	
1337		1	2	0	R	H	
1338		1	2	0	R	H	
1339		1	2	0	R	H	
1340		1	2	0	R	H	
1341		1	2	0	R	H	
1342		2	2	1	-	H	

Table 1.123

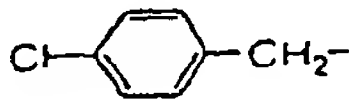
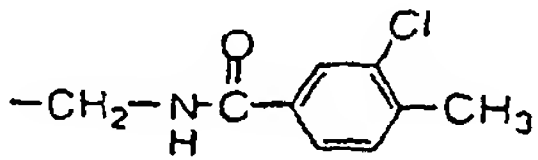

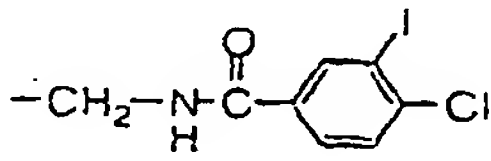

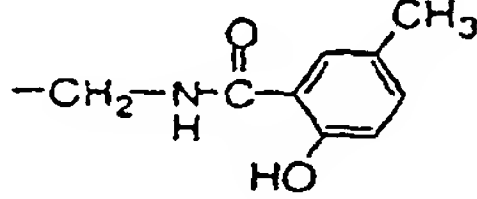
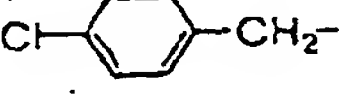
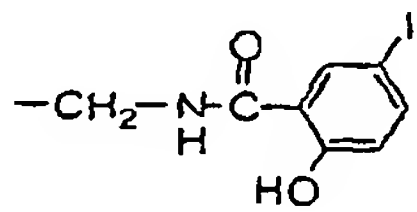

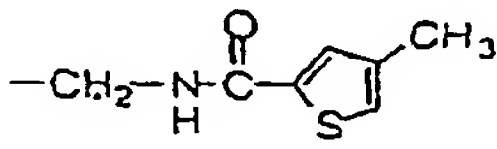

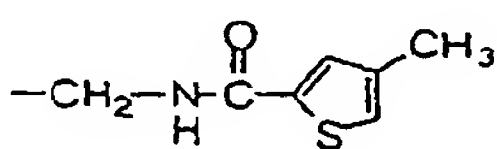
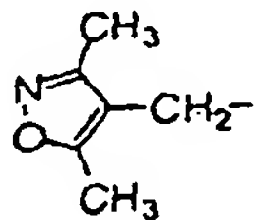
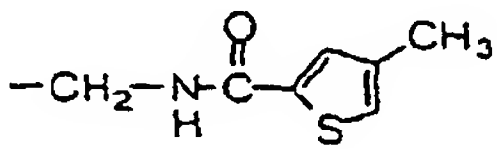
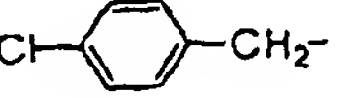
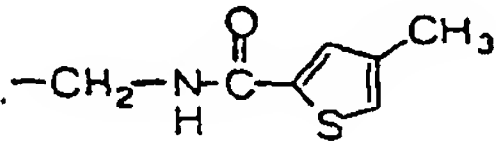
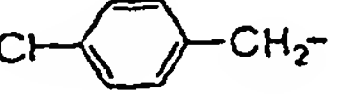
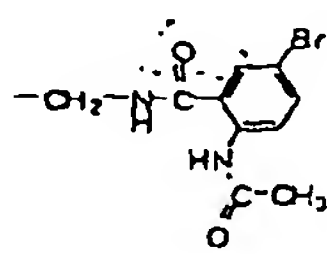
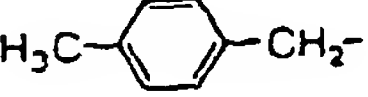
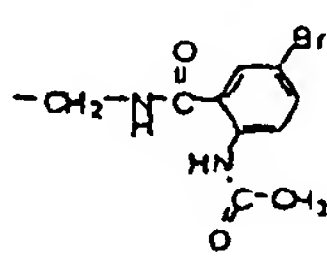
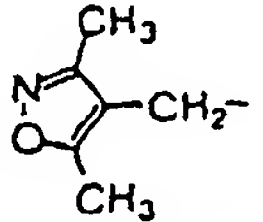
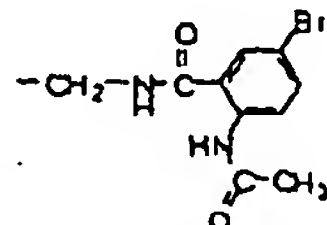
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1343		2	2	1	-	H	
1344		2	2	1	-	H	
1345		2	2	1	-	H	
1346		2	2	1	-	H	
1347		1	2	0	R	H	
1348		1	2	0	R	H	
1349		1	2	0	R	H	
1350		2	2	1	-	H	
1351		1	2	0	R	H	
1352		1	2	0	R	H	
1353		1	2	0	R	H	

Table 1.124

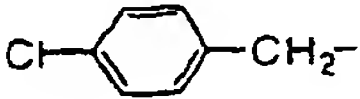
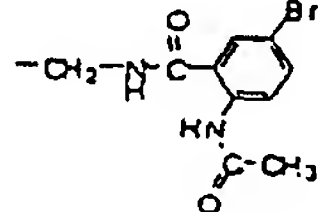
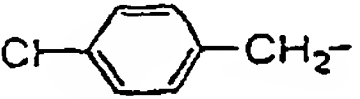
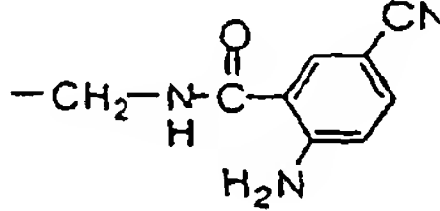
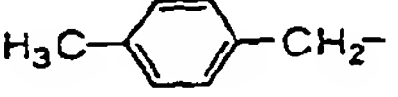
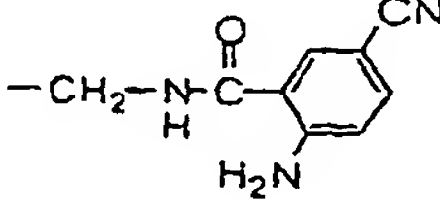
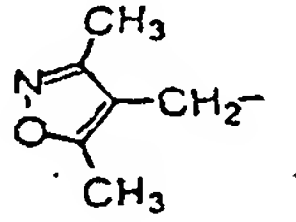
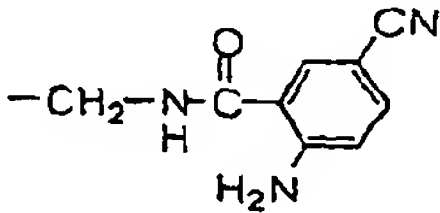

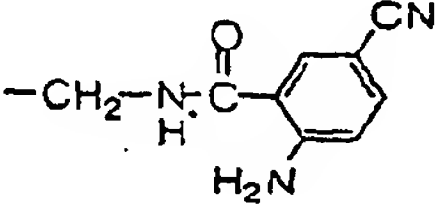
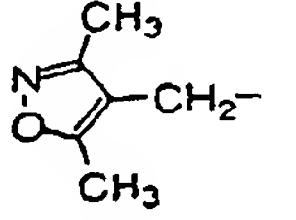
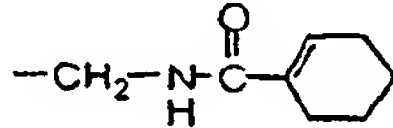
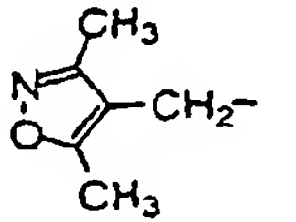
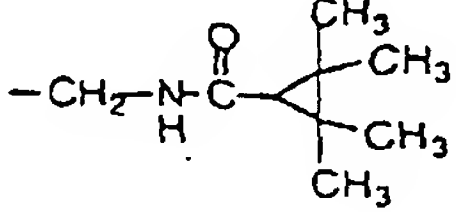

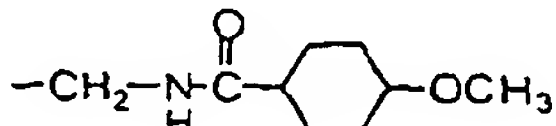
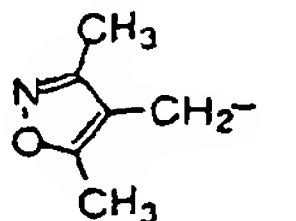
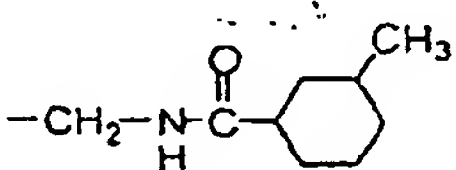
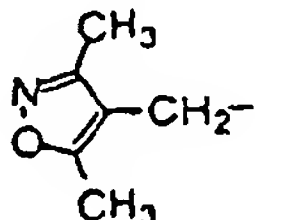
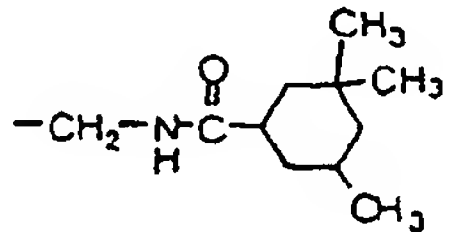
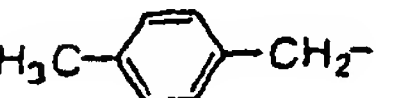
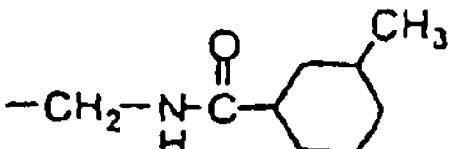
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_i -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1354		2	2	1	-	H	
1355		1	2	0	R	H	
1356		1	2	0	R	H	
1357		1	2	0	R	H	
1358		2	2	1	-	H	
1359		1	2	0	R	H	
1360		1	2	0	R	H	
1361		1	2	0	R	H	
1362		1	2	0	R	H	
1363		1	2	0	R	H	
1364		1	2	0	R	H	

Table 1.125

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_l -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1365		1	2	0	R	H	
1366		1	2	0	R	H	
1367		1	2	0	R	H	
1368		1	2	0	R	H	
1369		1	2	0	R	H	
1370		1	2	0	R	H	
1371		1	2	0	R	H	
1372		1	2	0	R	H	
1373		1	2	0	R	H	
1374		1	2	0	R	H	
1375		1	2	0	R	H	

Table 1.126

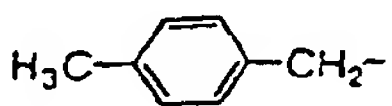
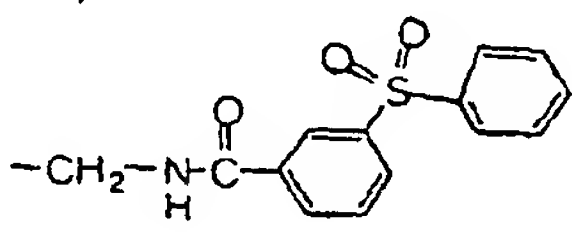

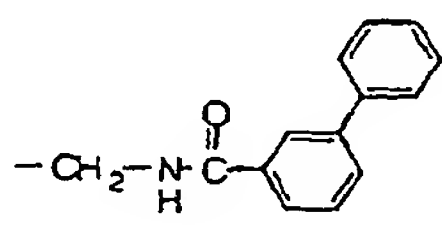
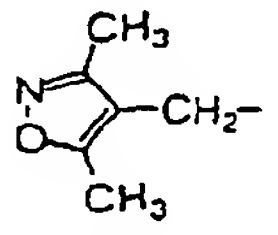
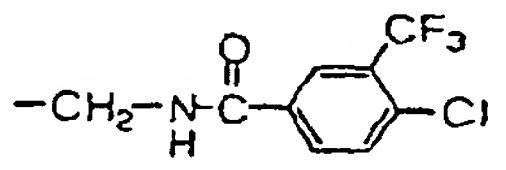
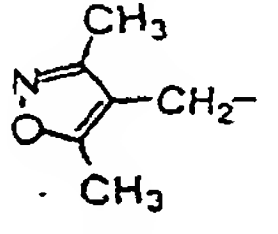
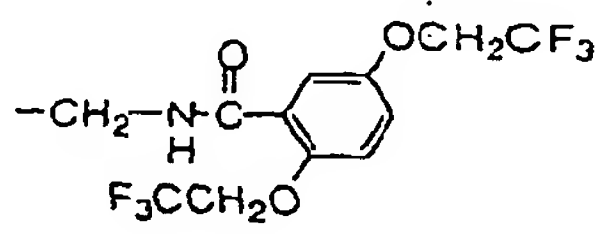
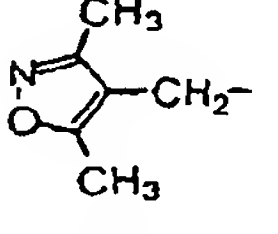
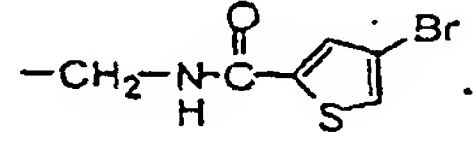
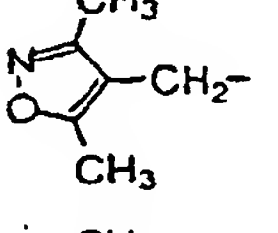
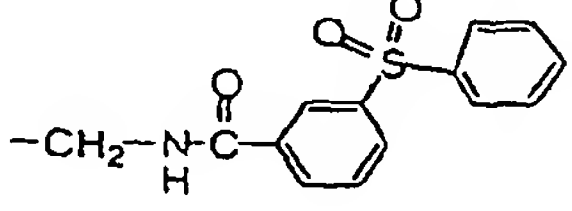
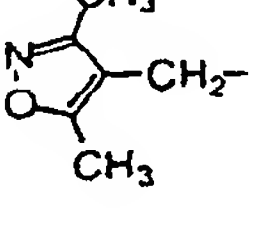
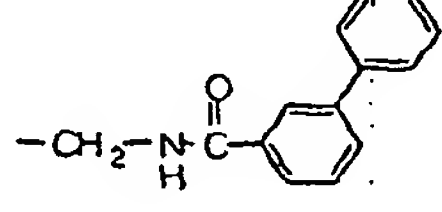
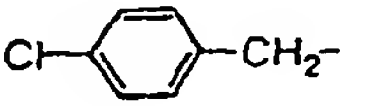
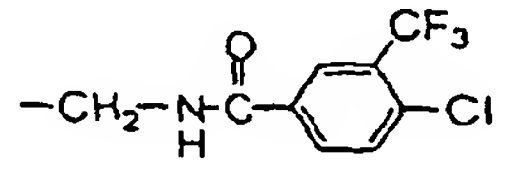
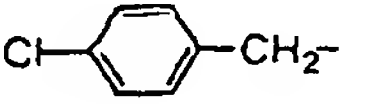
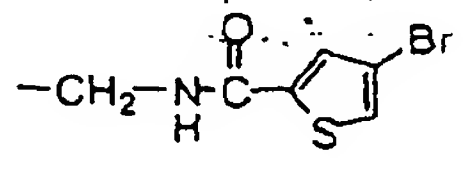
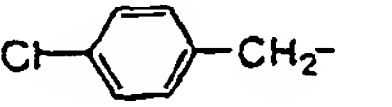
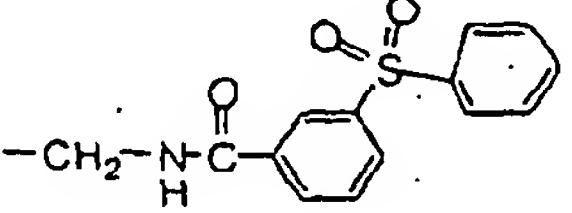
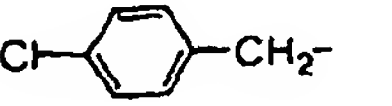
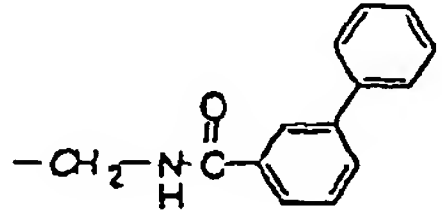
Compd. No.	$\begin{array}{c} R^1 \\ \\ R^2 \end{array} \text{---} (\text{CH}_2)_j \text{---}$	k	m	n	chirality	R^3	$-(\text{CH}_2)_p \text{---} \begin{array}{c} R^4 \\ \\ R^5 \end{array} \text{---} (\text{CH}_2)_q \text{---} \text{G---} R^6$
1376		1	2	0	R	H	
1377		1	2	0	R	H	
1378		1	2	0	R	H	
1379		1	2	0	R	H	
1380		1	2	0	R	H	
1381		1	2	0	R	H	
1382		1	2	0	R	H	
1383		2	2	1	-	H	
1384		2	2	1	-	H	
1385		2	2	1	-	H	
1386		2	2	1	-	H	

Table 1.127

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1387		1	2	0	R	H	
1388		1	2	0	R	H	
1389		1	2	0	R	H	
1390		1	2	0	R	H	
1391		1	2	0	R	H	
1392		1	2	0	R	H	
1393		1	2	0	R	H	
1394		1	2	0	R	H	
1395		1	2	0	R	H	
1396		1	2	0	R	H	
1397		1	2	0	R	H	

Table 1.128

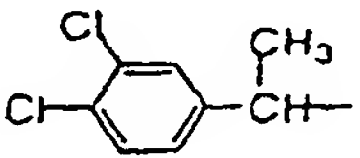
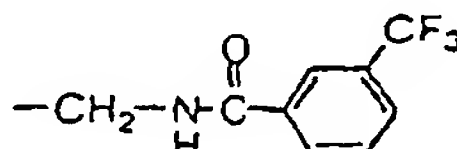
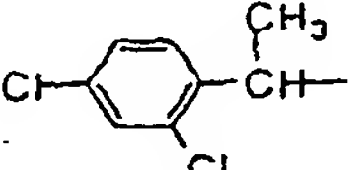
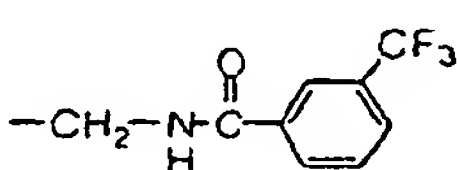
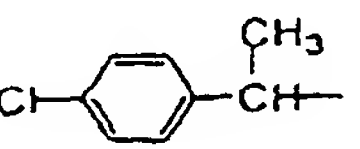
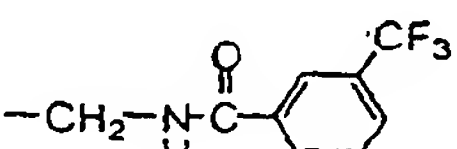
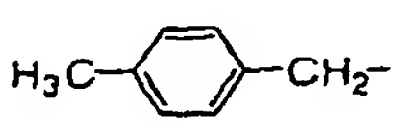
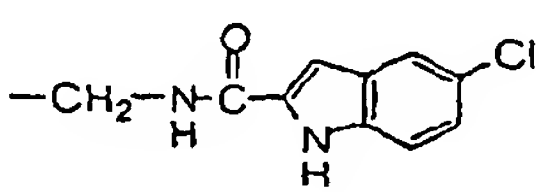

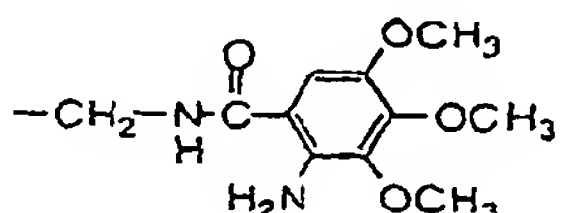
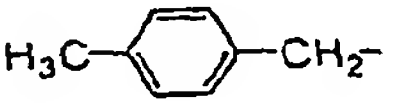
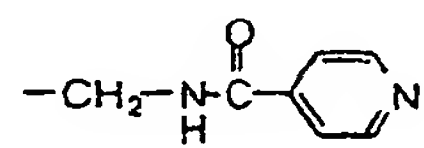

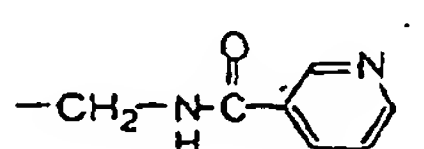

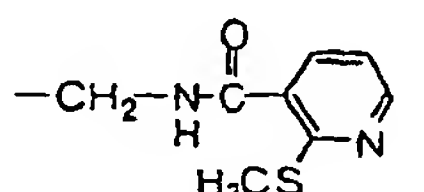
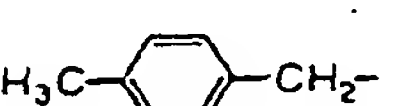
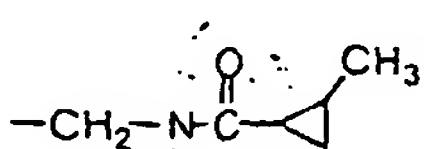

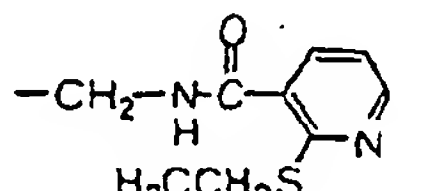
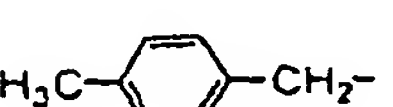
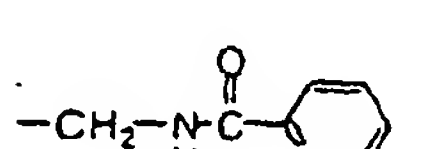
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1398		1	2	0	R	H	
1399		1	2	0	R	H	
1400		1	2	0	R	H	
1401		1	2	0	R	H	
1402		1	2	0	R	H	
1403		1	2	0	R	H	
1404		1	2	0	R	H	
1405		1	2	0	R	H	
1406		1	2	0	R	H	
1407		1	2	0	R	H	
1408		1	2	0	R	H	

Table 1.129

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_l$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1409		1	2	0	R	H	
1410		1	2	0	R	H	
1411		1	2	0	R	H	
1412		1	2	0	R	H	
1413		1	2	0	R	H	
1414		2	2	1	-	H	
1415		1	2	0	R	H	
1416		1	2	0	R	H	
1417		1	2	0	R	H	
1418		2	2	1	-	H	
1419		1	2	0	R	H	

Table 1.130

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1420		1	2	0	R	H	
1421		1	2	0	R	H	
1422		2	2	1	-	H	
1423		1	2	0	R	H	
1424		1	2	0	R	H	
1425		1	2	0	R	H	
1426		2	2	1	-	H	
1427		2	2	1	-	H	
1428		2	2	1	-	H	
1429		2	2	1	-	H	
1430		2	2	1	-	H	

Table 1.131

Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ (CH_2)_l- \\ \diagdown \\ R^2 \end{matrix}$	k	m	n	chirality	R^3	$-(CH_2)_p-\overset{\overset{R^4}{ }}{\underset{\underset{R^5}{ }}{C}}-(CH_2)_q-G-R^6$
1431		2	2	1	-	H	
1432		2	2	1	-	H	
1433		2	2	1	-	H	
1434		2	2	1	-	H	
1435		2	2	1	-	H	
1436		2	2	1	-	H	
1437		2	2	1	-	H	
1438		2	2	1	-	H	
1439		2	2	1	-	H	
1440		2	2	1	-	H	
1441		2	2	1	-	H	

Table 1.132

Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ R^2 \end{matrix} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
1442	$H_3CCH_2 - \text{C}_6H_4 - CH_2 -$	2	2	1	-	H	$-CH_2 - NH - C(=O) - \text{C}_6H_3(O) - NH - CH_2 - \text{C}_6H_4 - CH_2CH_3$
1443	$(H_3C)_2CH - \text{C}_6H_4 - CH_2 -$	2	2	1	-	H	$-CH_2 - NH - C(=O) - \text{C}_6H_3(O) - NH - CH_2 - \text{C}_6H_4 - CH(CH_3)_2$
1444	$H_3C(CH_2)_2O - \text{C}_6H_4 - CH_2 -$	2	2	1	-	H	$-CH_2 - NH - C(=O) - \text{C}_6H_3(O) - NH - CH_2 - \text{C}_6H_4 - O(CH_2)_2CH_3$
1445	$H_3CCH_2 - \text{C}_6H_4 - CH_2 -$	2	2	1	-	H	$-CH_2 - NH - C(=O) - \text{C}_6H_3(Br) - NH - CH_2 - \text{C}_6H_4 - CH_2CH_3$
1446	$(H_3C)_2CH - \text{C}_6H_4 - CH_2 -$	2	2	1	-	H	$-CH_2 - NH - C(=O) - \text{C}_6H_3(Br) - NH - CH_2 - \text{C}_6H_4 - CH(CH_3)_2$
1447	$H_3C(CH_2)_2O - \text{C}_6H_4 - CH_2 -$	2	2	1	-	H	$-CH_2 - NH - C(=O) - \text{C}_6H_3(Br) - NH - CH_2 - \text{C}_6H_4 - O(CH_2)_2CH_3$
1448	$H_3CS - \text{C}_6H_4 - CH_2 -$	2	2	1	-	H	$-CH_2 - NH - C(=O) - \text{C}_6H_3(Br) - NH - CH_2 - \text{C}_6H_4 - SCH_3$
1449	$H_3CCH_2 - \text{C}_6H_4 - CH_2 -$	2	2	1	-	H	$-CH_2 - NH - C(=O) - \text{C}_6H_4 - CF_3$
1450	$(H_3C)_2CH - \text{C}_6H_4 - CH_2 -$	2	2	1	-	H	$-CH_2 - NH - C(=O) - \text{C}_6H_4 - CF_3$
1451	$(H_3CCH_2)_2N - \text{C}_6H_4 - CH_2 -$	2	2	1	-	H	$-CH_2 - N - C(=O) - \text{C}_6H_4 - CF_3$
1452	$H_3CO - \text{C}_6H_3(OH) - CH_2 -$	2	2	1	-	H	$-CH_2 - NH - C(=O) - \text{C}_6H_4 - CF_3$

Table 1.133

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_k \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ (CH_2)_q \\ \\ R^5 \end{array} G-R^6$
1453		2	2	1	-	H	
1454		2	2	1	-	H	
1455		2	2	1	-	H	
1456		2	2	1	-	H	
1457		2	2	1	-	H	
1458		2	2	1	-	H	
1459		2	2	1	-	H	
1460		2	2	1	-	H	
1461		2	2	1	-	H	
1462		2	2	1	-	H	
1463		2	1	1	-	H	

Table 1.134

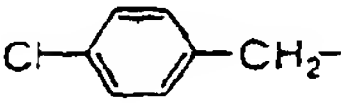
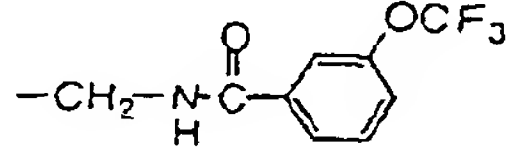
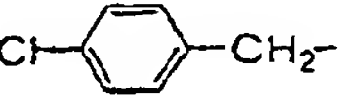
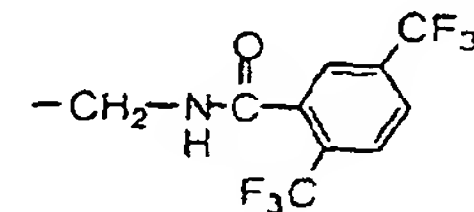
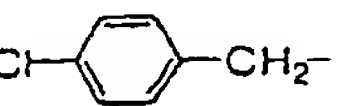
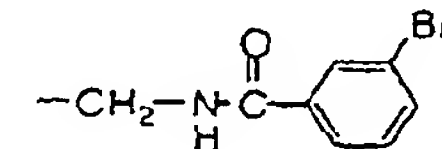
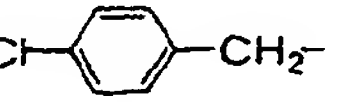
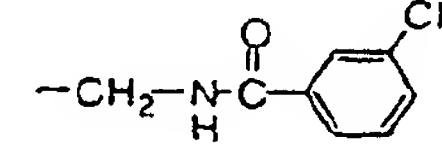
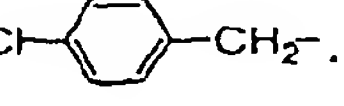
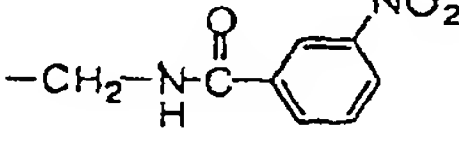
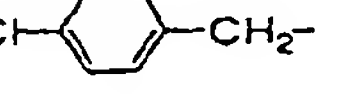
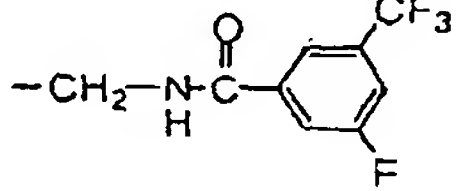
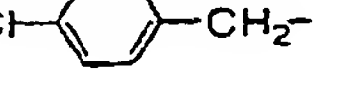
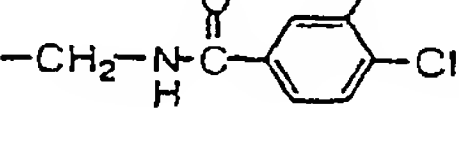
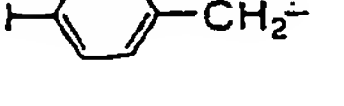
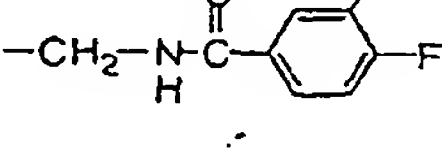
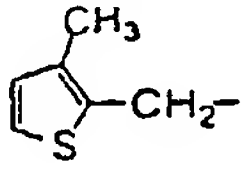
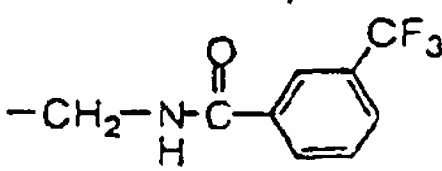
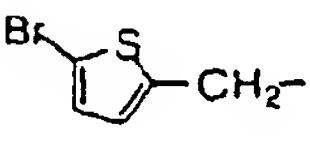
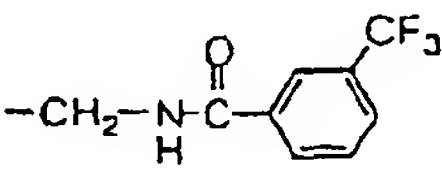
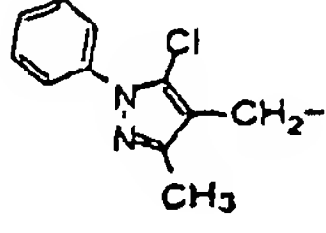
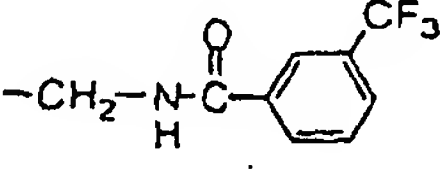
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1464		2	1	1	-	H	
1465		2	1	1	-	H	
1466		2	1	1	-	H	
1467		2	1	1	-	H	
1468		2	1	1	-	H	
1469		2	1	1	-	H	
1470		2	1	1	-	H	
1471		2	1	1	-	H	
1472		1	2	0	R	H	
1473		1	2	0	R	H	
1474		1	2	0	R	H	

Table 1.135

Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ R^2 \end{matrix} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
1475		1	2	0	R	H	
1476		1	2	0	R	H	
1477		1	2	0	R	H	
1478		1	2	0	R	H	
1479		1	2	0	R	H	
1480		1	2	0	R	H	
1481		1	2	0	R	H	
1482		1	2	0	R	H	
1483		1	2	0	R	H	
1484		1	2	0	R	H	
1485		1	2	0	R	H	

Table 1.136

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_i$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1486		1	2	0	R	H	
1487		1	2	0	R	H	
1488		1	2	0	R	H	
1489		1	2	0	R	H	
1490		1	2	0	R	H	
1491		1	2	0	R	H	
1492		1	2	0	R	H	
1493		1	2	0	R	H	
1494		1	2	0	R	H	
1495		1	2	0	R	H	
1496		1	2	0	R	H	

Table 1.137

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_i$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q G-R^6$
1497		1	2	0	R	H	
1498		1	2	0	R	H	
1499		1	2	0	R	H	
1500		1	2	0	R	H	
1501		1	2	0	R	H	
1502		1	2	0	R	H	
1503		1	2	0	R	H	
1504		1	2	0	R	H	
1505		1	2	0	R	H	
1506		2	1	1	-	H	
1507		2	1	1	-	H	

Table 1.138

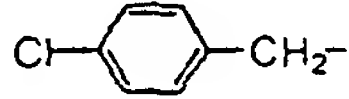
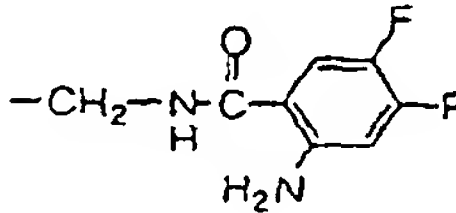
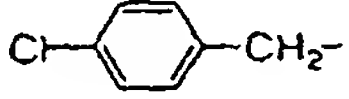
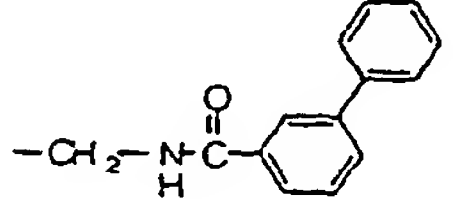
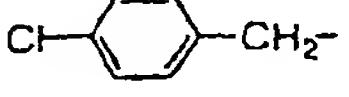
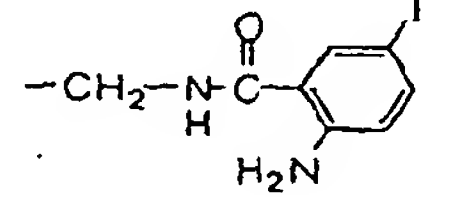
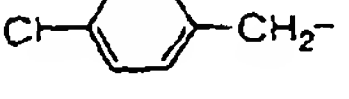
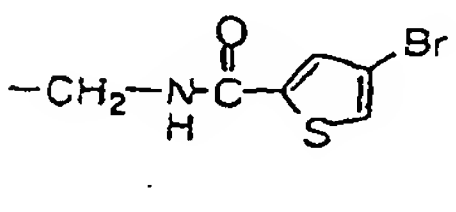
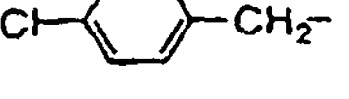
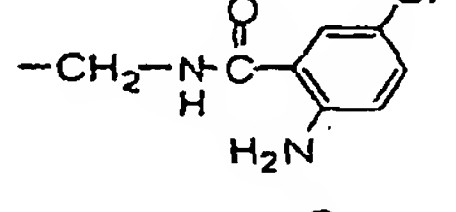
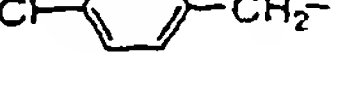
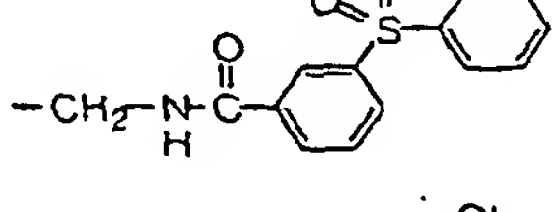
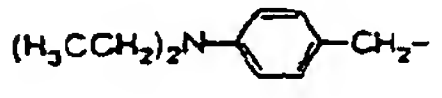
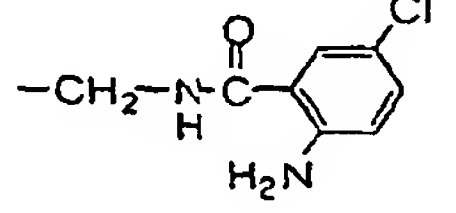
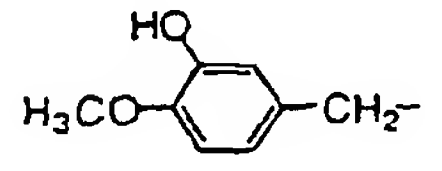
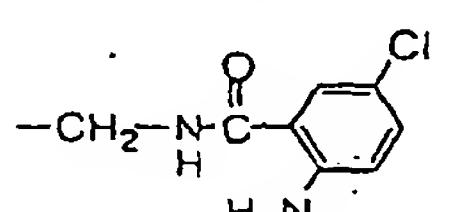
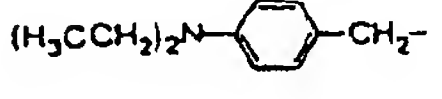
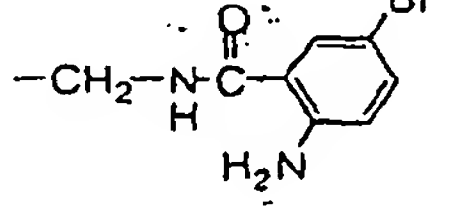
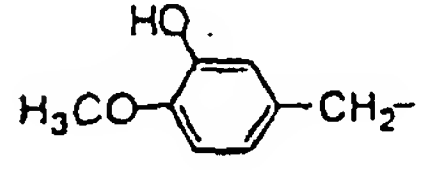
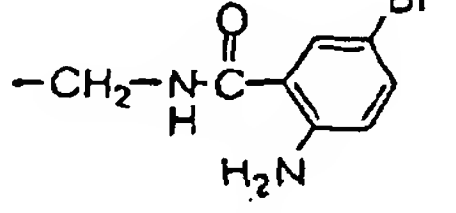
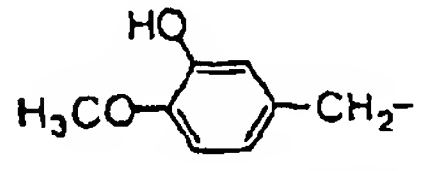
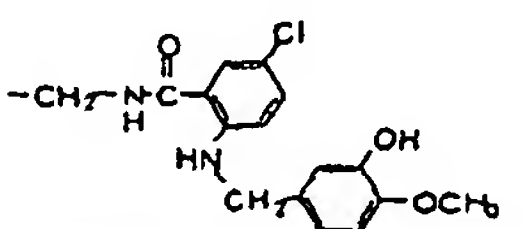
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1508		2	1	1	-	H	
1509		2	1	1	-	H	
1510		2	1	1	-	H	
1511		2	1	1	-	H	
1512		2	1	1	-	H	
1513		2	1	1	-	H	
1514		2	2	1	-	H	
1515		2	2	1	-	H	
1516		2	2	1	-	H	
1517		2	2	1	-	H	
1518		2	2	1	-	H	

Table 1.139

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_l$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1519		2	2	1	-	H	
1520		1	2	0	R	H	
1521		1	2	0	R	H	
1522		1	2	0	R	H	
1523		1	2	0	R	H	
1524		1	2	0	R	H	
1525		1	2	0	R	H	
1526		1	2	0	R	H	
1527		1	2	0	R	H	
1528		1	2	0	R	H	
1529		1	2	0	R	H	

Table 1.140

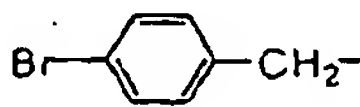
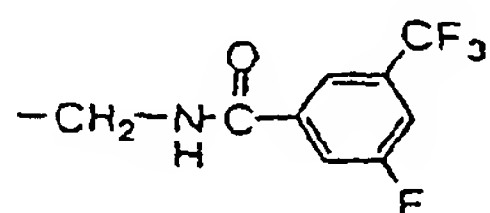
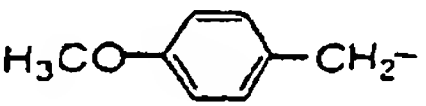
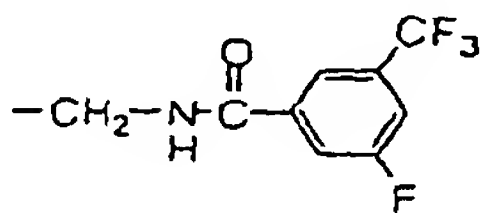
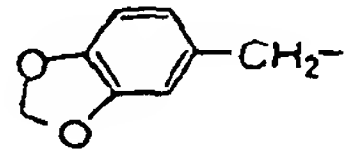
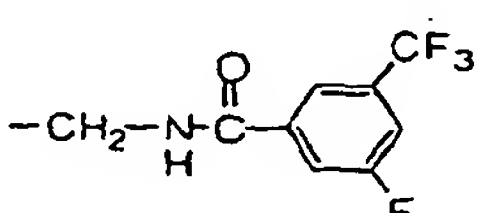
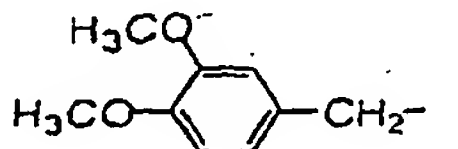
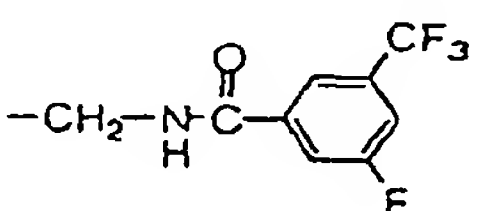
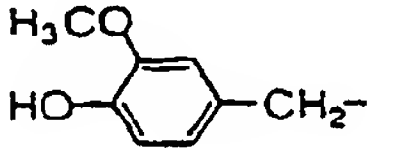
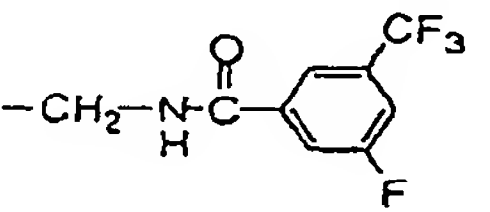
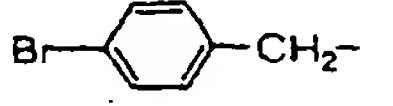
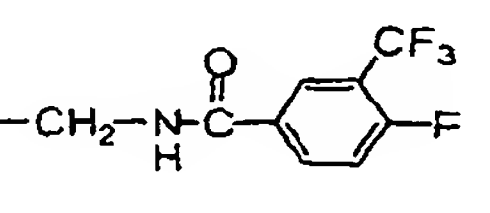
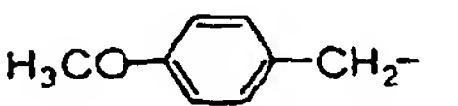
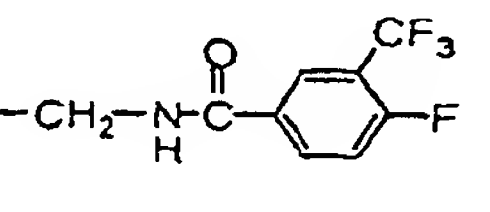
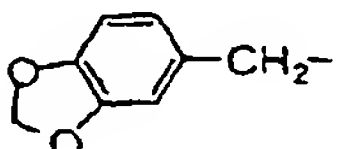
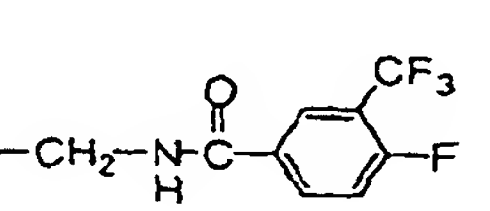
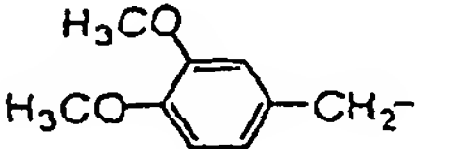
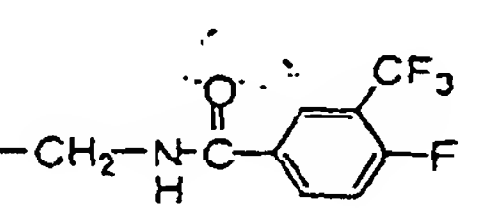
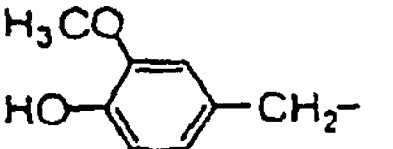
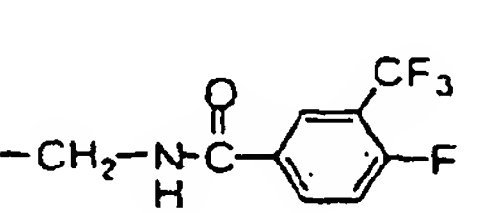
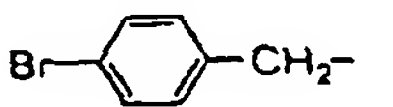
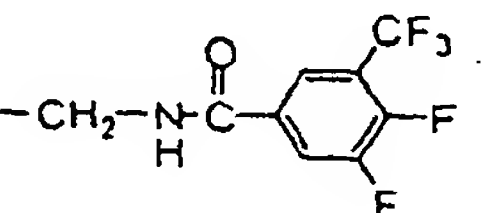
Compd. No.	$\begin{array}{c} R^1 \\ \\ R^2 \end{array} - (CH_2)_k -$	k	m	n	chirality	R^3	$-(CH_2)_p - \begin{array}{c} R^4 \\ \\ R^5 \end{array} - (CH_2)_q - G - R^6$
1530		1	2	0	R	H	
1531		1	2	0	R	H	
1532		1	2	0	R	H	
1533		1	2	0	R	H	
1534		1	2	0	R	H	
1535		1	2	0	R	H	
1536		1	2	0	R	H	
1537		1	2	0	R	H	
1538		1	2	0	R	H	
1539		1	2	0	R	H	
1540		1	2	0	R	H	

Table 1.141


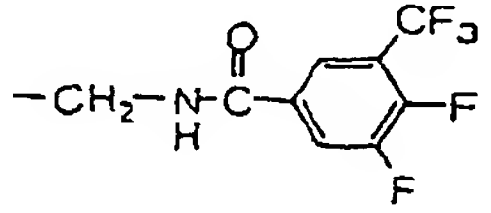
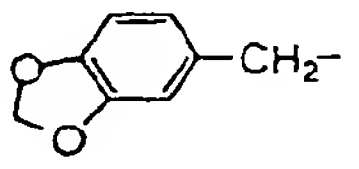
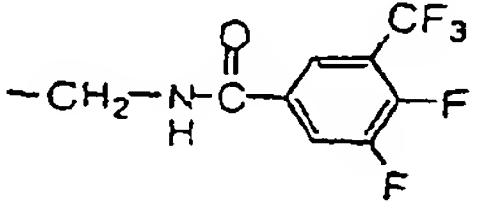
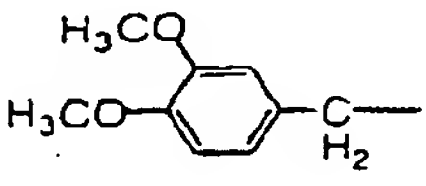
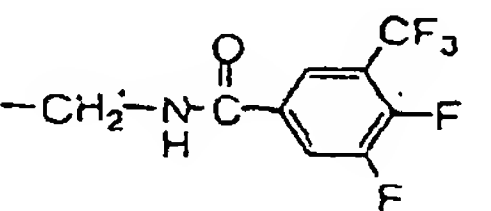
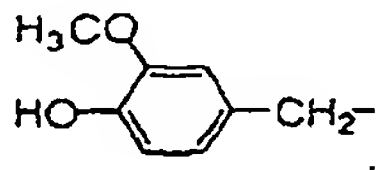
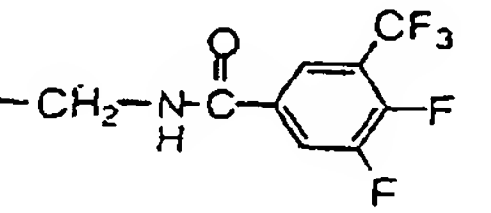
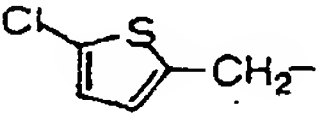
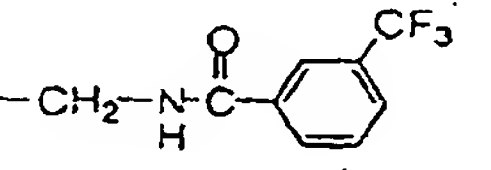
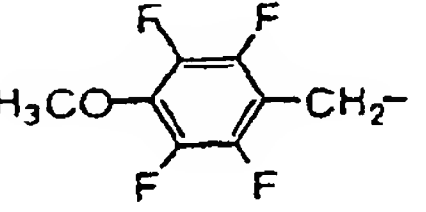
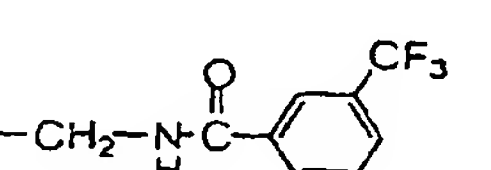
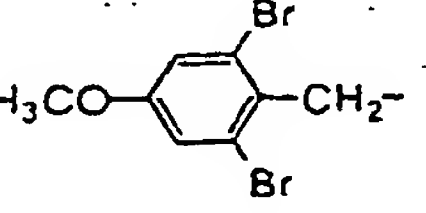
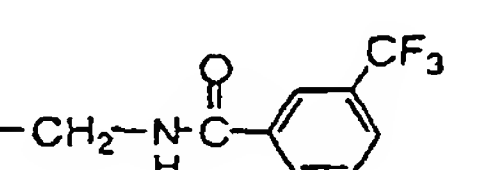
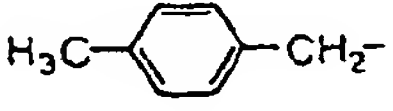
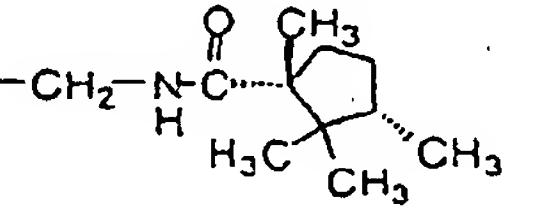
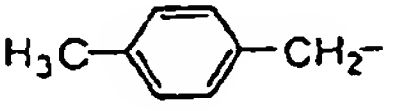
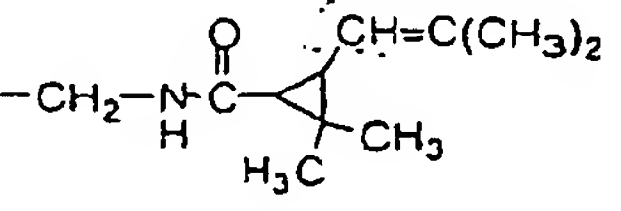
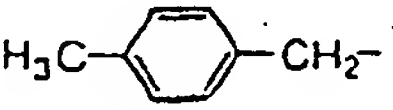
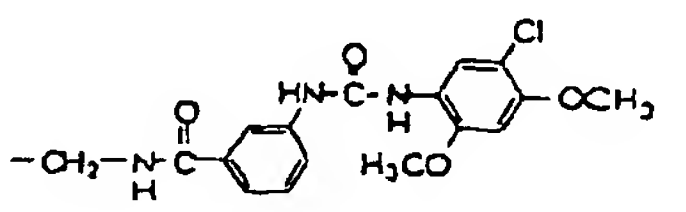
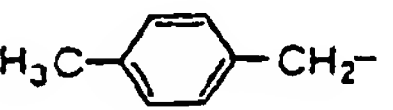
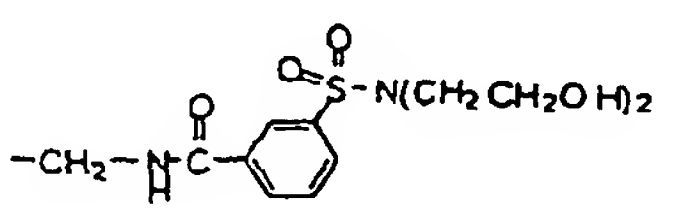
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_k \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1541		1	2	0	R	H	
1542		1	2	0	R	H	
1543		1	2	0	R	H	
1544		1	2	0	R	H	
1545		1	2	0	R	H	
1546		1	2	0	R	H	
1547		1	2	0	R	H	
1548		1	2	0	R	H	
1549		1	2	0	R	H	
1550		1	2	0	R	H	
1551		1	2	0	R	H	

Table 1.142

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1552		1	2	0	R	H	
1553		1	2	0	R	H	
1554		1	2	0	R	H	
1555		1	2	0	R	H	
1556		1	2	0	R	H	
1557		1	2	0	R	H	
1558		1	2	0	R	H	
1559		1	2	0	R	H	
1560		1	2	0	R	H	
1561		1	2	0	R	H	
1562		1	2	0	R	H	

Table 1.143

Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (\text{CH}_2)_k \text{---}$	k	m	n	chirality	R^3	$-(\text{CH}_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} \text{---} (\text{CH}_2)_q \text{---} \text{G} \text{---} R^6$
1563		1	2	0	R	H	
1564		1	2	0	R	H	
1565		1	2	0	R	H	
1566		1	2	0	R	H	
1567		1	2	0	R	H	
1568		1	2	0	R	H	
1569		1	2	0	R	H	
1570		2	2	1	-	H	
1571		2	2	1	-	H	
1572		2	2	1	-	H	
1573		2	2	1	-	H	

Table 1.144

Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (\text{CH}_2)_k \text{---}$	k	m	n	chirality	R^3	$-(\text{CH}_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} \text{---} (\text{CH}_2)_q \text{---} \text{G---} R^6$
1574		2	2	1	-	H	
1575		2	2	1	-	H	
1576		2	2	1	-	H	
1577		2	2	1	-	H	
1578		2	2	1	-	H	
1579		2	2	1	-	H	
1580		2	2	1	-	H	
1581		2	2	1	-	H	
1582		2	2	1	-	H	
1583		1	2	0	R	H	
1584		1	2	0	R	H	

Table 1.145

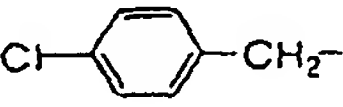
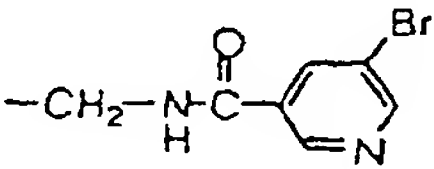
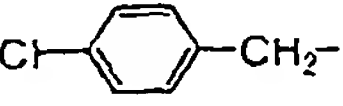
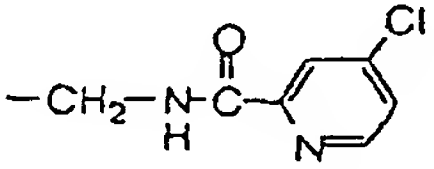
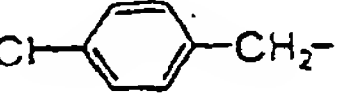
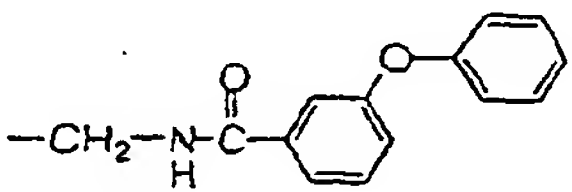
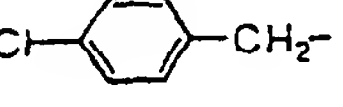
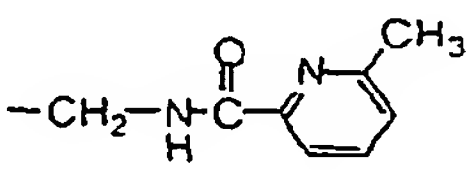
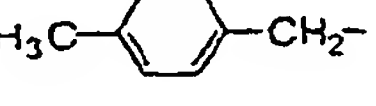
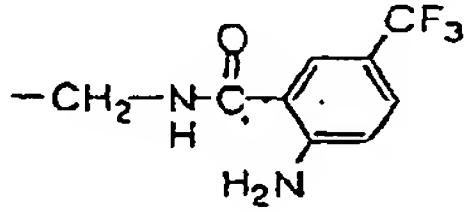
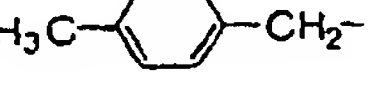
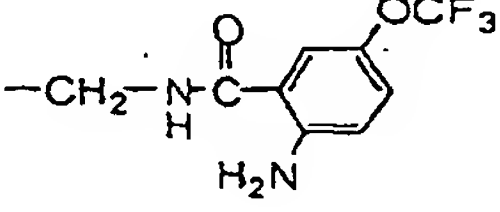
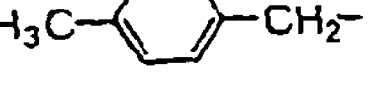
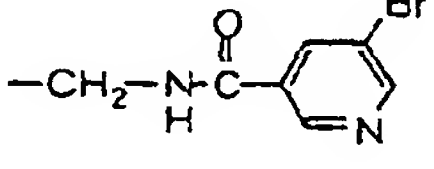
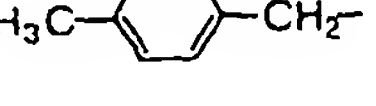
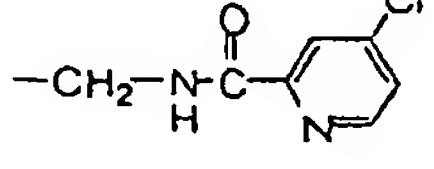
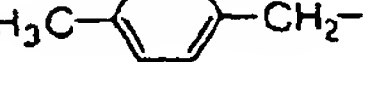
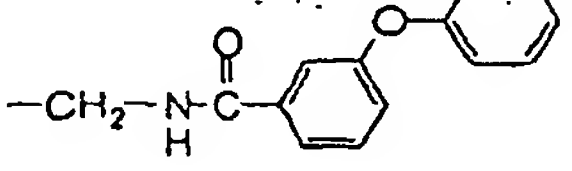
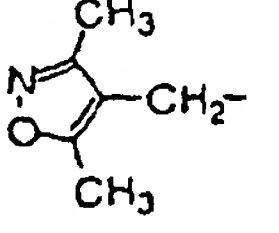
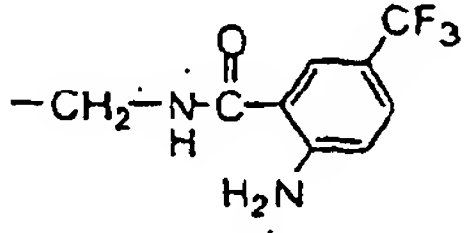
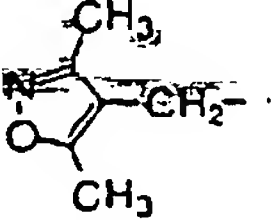
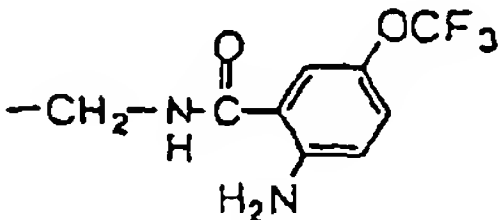
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p-\overset{\overset{R^4}{ }}{\underset{\underset{R^5}{ }}{C}}-(CH_2)_q-G-R^6$
1585		1	2	0	R	H	
1586		1	2	0	R	H	
1587		1	2	0	R	H	
1588		1	2	0	R	H	
1589		1	2	0	R	H	
1590		1	2	0	R	H	
1591		1	2	0	R	H	
1592		1	2	0	R	H	
1593		1	2	0	R	H	
1594		1	2	0	R	H	
1595		1	2	0	R	H	

Table 1.146

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_l \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1596		1	2	0	R	H	
1597		1	2	0	R	H	
1598		1	2	0	R	H	
1599		1	2	0	R	H	
1600		2	2	1	-	H	
1601		2	2	1	-	H	
1602		2	2	1	-	H	
1603		2	2	1	-	H	
1604		2	2	1	-	H	
1605		2	2	1	-	H	
1606		1	2	0	R	H	

Table 1.147

Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ (CH_2)_j \\ \diagdown \\ R^2 \end{matrix}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
1607		1	2	0	R	H	
1608		1	2	0	R	H	
1609		2	2	1	-	H	
1610		2	2	1	-	H	
1611		2	2	1	-	H	
1612		2	2	1	-	H	
1613		2	2	1	-	H	
1614		1	2	0	R	H	
1615		2	2	1	-	H	
1616		2	2	1	-	H	
1617		2	2	1	-	H	

Table 1.148

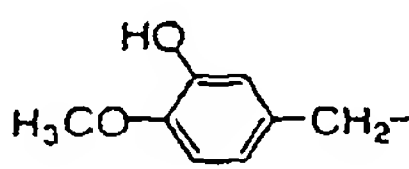
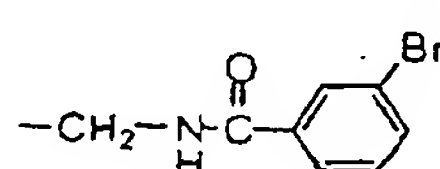
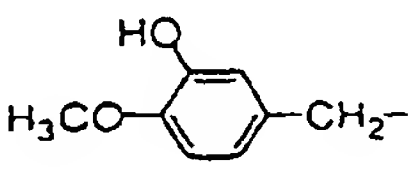
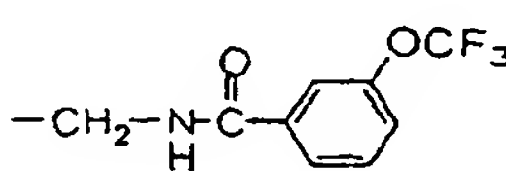
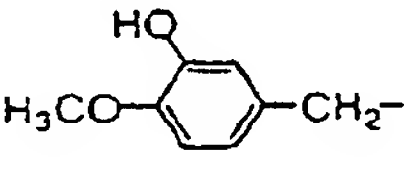
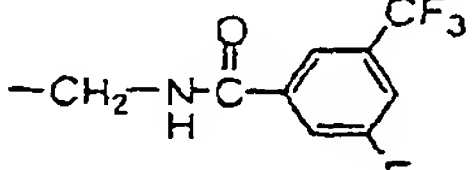
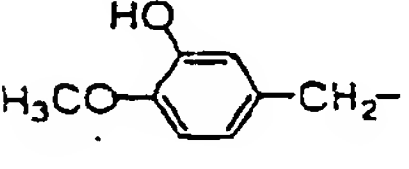
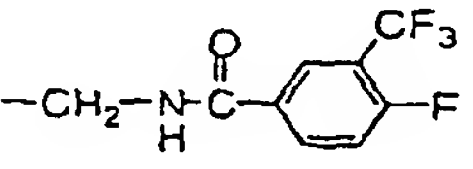
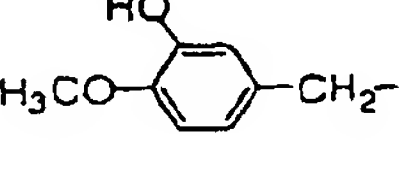
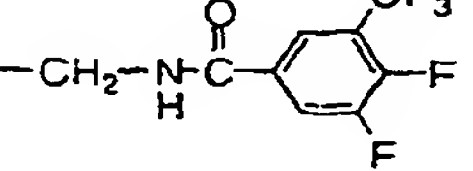
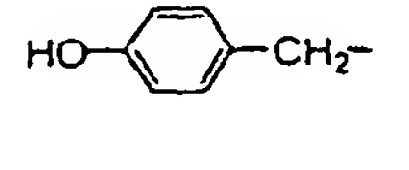
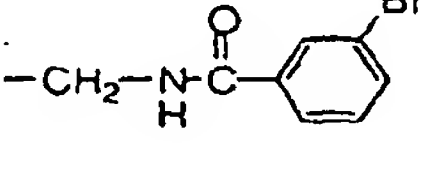
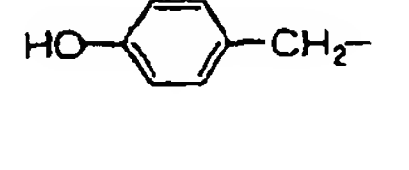
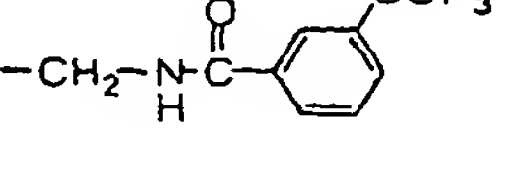
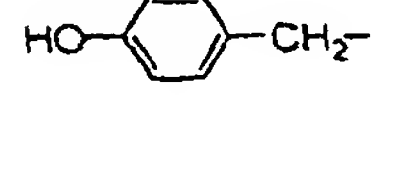
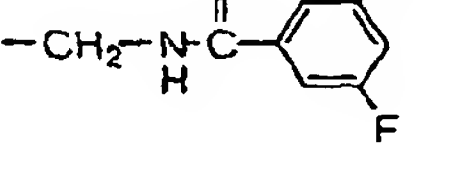
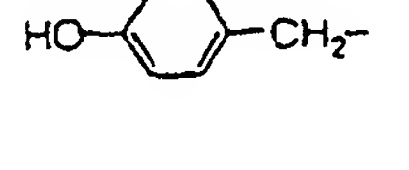
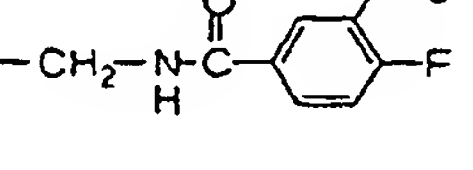
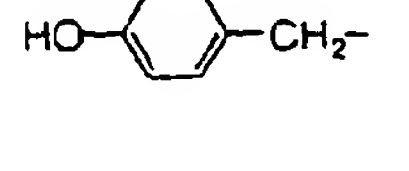
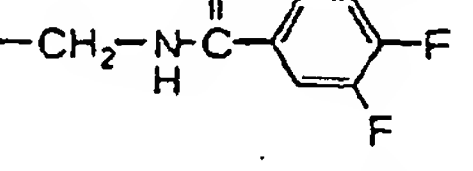
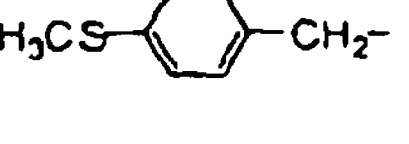
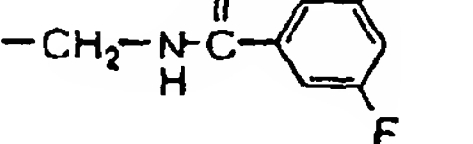
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1618		1	2	0	R	H	
1619		1	2	0	R	H	
1620		1	2	0	R	H	
1621		1	2	0	R	H	
1622		1	2	0	R	H	
1623		1	2	0	R	H	
1624		1	2	0	R	H	
1625		1	2	0	R	H	
1626		1	2	0	R	H	
1627		1	2	0	R	H	
1628		1	2	0	R	H	

Table 1.149


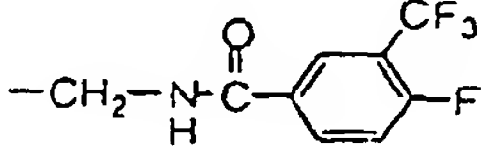
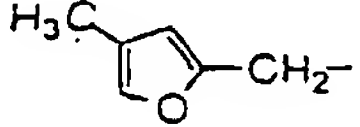
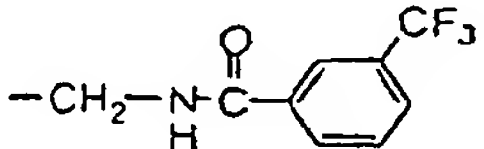
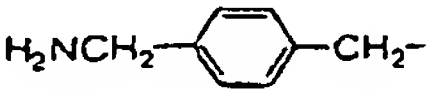
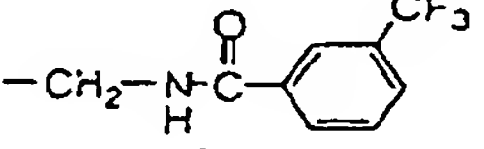
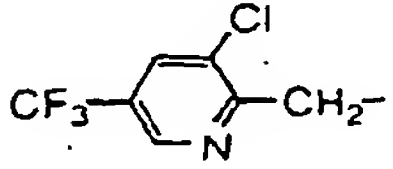
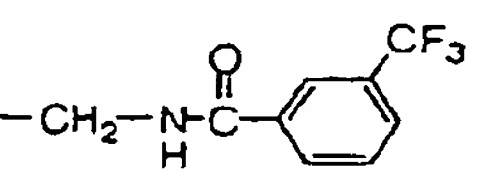
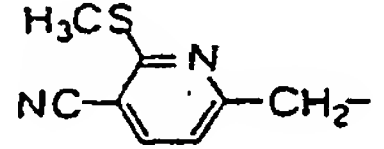
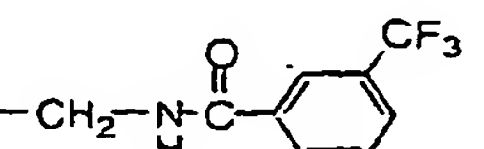
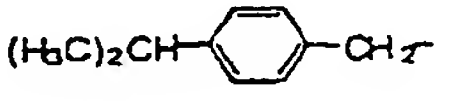
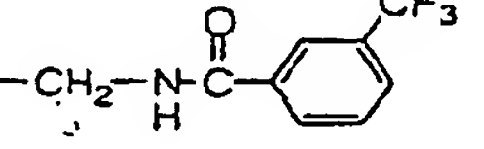
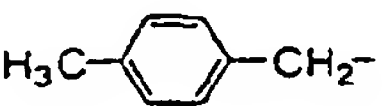
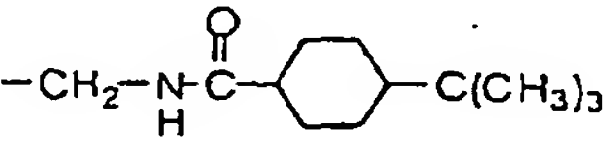
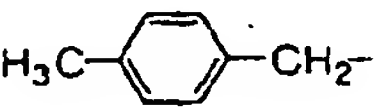
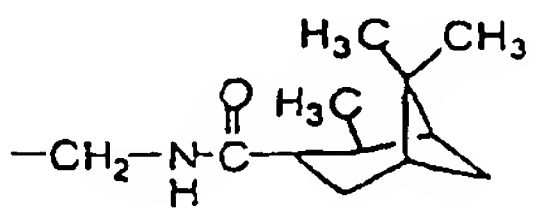
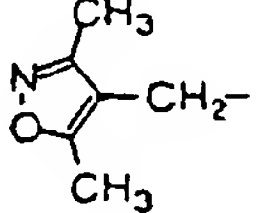
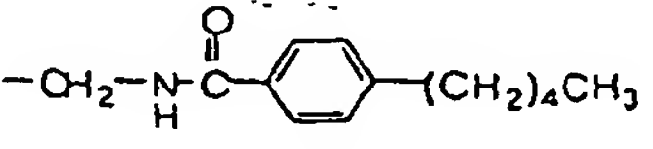
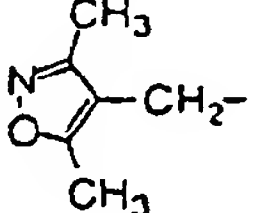
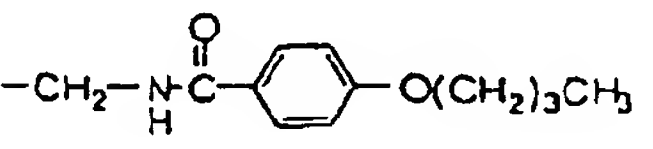
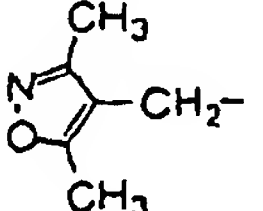
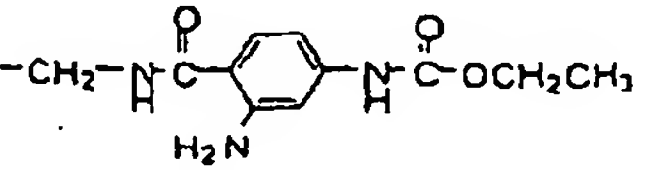
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1629		1	2	0	R	H	
1630		1	2	0	R	H	
1631		1	2	0	R	H	
1632		1	2	0	R	H	
1633		1	2	0	R	H	
1634		1	2	0	R	H	
1635		1	2	0	R	H	
1636		1	2	0	R	H	
1637		1	2	0	R	H	
1638		1	2	0	R	H	
1639		1	2	0	R	H	

Table 1.150

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1640		1	2	0	R	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{NH}-(\text{CH}_2)_3\text{CH}_3$
1641		1	2	0	R	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{OCF}_2\text{CHClF}$
1642		1	2	0	R	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{NO}_2$
1643		1	2	0	R	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{C}_6\text{H}_5$
1644		1	2	0	R	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{C}(=\text{O})-\text{C}_6\text{H}_5$
1645		1	2	0	R	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{CF}_3$
1646		1	2	0	R	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{CF}_3$
1647	$\text{H}_3\text{C}(\text{CH}_2)_3-\text{C}_6\text{H}_4-\text{CH}_2-$	2	2	1	-	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{CF}_3$
1648	$\text{H}_3\text{C}(\text{CH}_2)_3-\text{C}_6\text{H}_4-\text{CH}_2-$	1	2	0	R	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{CF}_3$
1649	$\text{H}_3\text{C}(\text{CH}_2)_2-\text{C}_6\text{H}_4-\text{CH}_2-$	2	2	1	-	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{CF}_3$
1650	$\text{H}_3\text{C}(\text{CH}_2)_2-\text{C}_6\text{H}_4-\text{CH}_2-$	1	2	0	R	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{CF}_3$

Table 1.151

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_l \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1651	$H_3C(CH_2)_3-\text{C}_6\text{H}_4-\text{CH}_2-$	2	2	1	-	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_3(\text{Br})-\text{NH}-\text{CH}_2-\text{C}_6\text{H}_4-(CH_2)_3CH_3$
1652	$H_3C(CH_2)_3-\text{C}_6\text{H}_4-\text{CH}_2-$	2	2	1	-	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_3(\text{Br})-\text{NH}_2$
1653	$H_3C(CH_2)_2-\text{C}_6\text{H}_4-\text{CH}_2-$	2	2	1	-	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_3(\text{Br})-\text{NH}-\text{CH}_2-\text{C}_6\text{H}_4-(CH_2)_2CH_3$
1654	$H_3C(CH_2)_2-\text{C}_6\text{H}_4-\text{CH}_2-$	2	2	1	-	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_3(\text{Br})-\text{NH}_2$
1655	$H_3C(CH_2)_3-\text{C}_6\text{H}_4-\text{CH}_2-$	2	2	1	-	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_3(\text{Cl})-\text{NH}-\text{CH}_2-\text{C}_6\text{H}_4-(CH_2)_3CH_3$
1656	$H_3C(CH_2)_3-\text{C}_6\text{H}_4-\text{CH}_2-$	2	2	1	-	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_3(\text{Cl})-\text{NH}_2$
1657	$H_3C(CH_2)_2-\text{C}_6\text{H}_4-\text{CH}_2-$	2	2	1	-	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_3(\text{Cl})-\text{NH}-\text{CH}_2-\text{C}_6\text{H}_4-(CH_2)_2CH_3$
1658	$H_3C(CH_2)_2-\text{C}_6\text{H}_4-\text{CH}_2-$	2	2	1	-	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_3(\text{Cl})-\text{NH}_2$
1659	$\text{Cl}-\text{C}_6\text{H}_4-\text{CH}_2-$	2	2	1	-	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_3(\text{Cl})-\text{NH}_2$
1660	$\text{Br}-\text{C}_6\text{H}_4-\text{CH}_2-$	1	2	0	R	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_3(\text{CF}_3)-\text{NH}_2$
1661	$\text{Br}-\text{C}_6\text{H}_4-\text{CH}_2-$	1	2	0	R	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_3(\text{OCF}_3)-\text{NH}_2$

Table 1.152

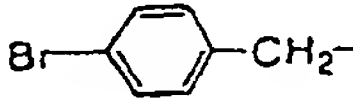
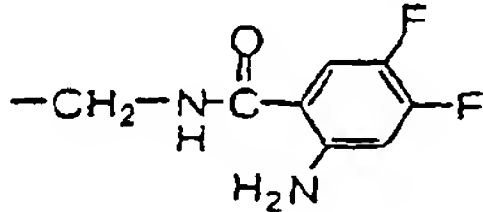
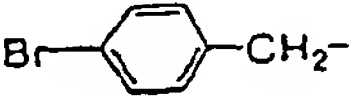
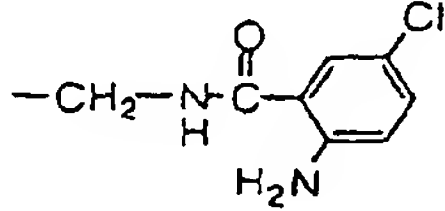
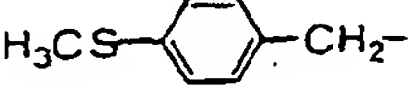
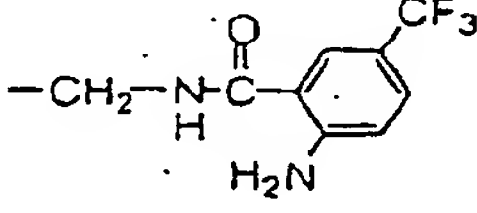

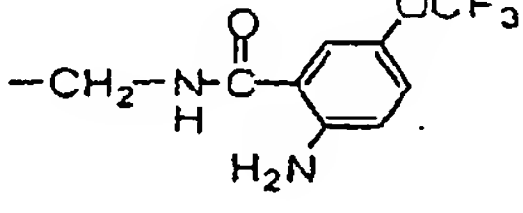

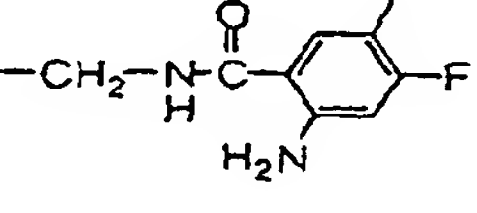
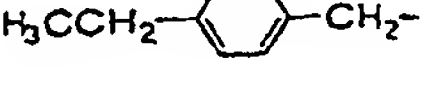
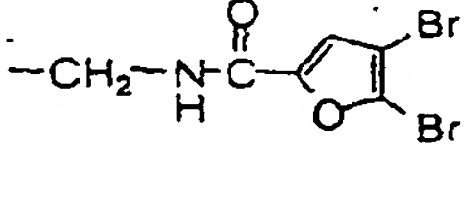
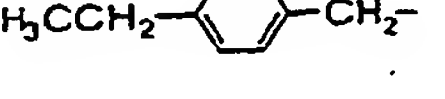
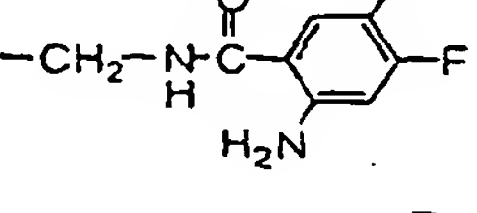
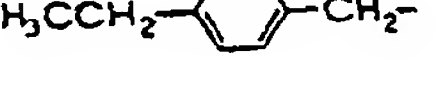
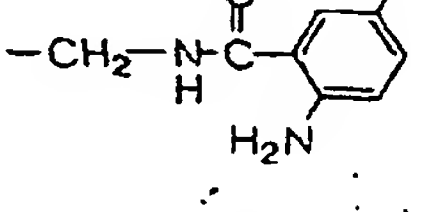
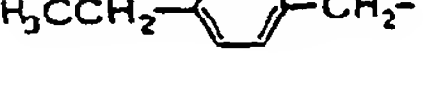
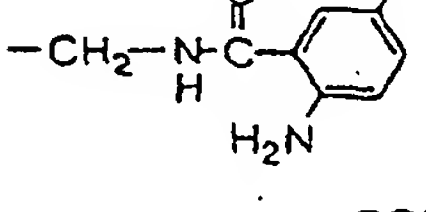
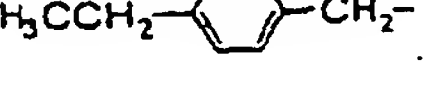
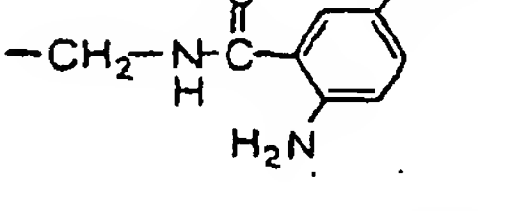
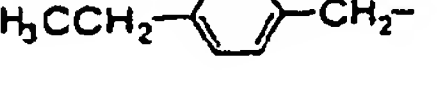
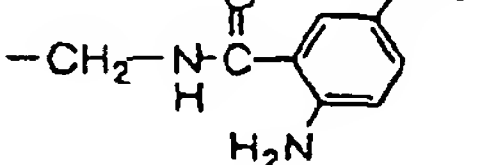
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1662		1	2	0	R	H	
1663		1	2	0	R	H	
1664		2	2	1	-	H	
1665		2	2	1	-	H	
1666		2	2	1	-	H	
1667		2	2	1	-	H	
1668		2	2	1	-	H	
1669		2	2	1	-	H	
1670		2	2	1	-	H	
1671		2	2	1	-	H	
1672		2	2	1	-	H	

Table 1.153

Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (CH_2)_l \text{---}$	k	m	n	chirality	R^3	$-(CH_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} \text{---} (CH_2)_q \text{---} G \text{---} R^6$
1673	$H_3CCH_2 \text{---} \text{C}_6H_4 \text{---} CH_2 \text{---}$	2	2	1	-	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6H_3(\text{Br})(\text{Cl})$
1674	$F \text{---} \text{C}_6H_4 \text{---} CH_2 \text{---}$	2	2	1	-	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_5H_2(\text{Br})_2\text{O}$
1675	$F \text{---} \text{C}_6H_4 \text{---} CH_2 \text{---}$	2	2	1	-	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6H_3(\text{F})_2\text{NH}_2$
1676	$F \text{---} \text{C}_6H_4 \text{---} CH_2 \text{---}$	2	2	1	-	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6H_3(\text{F})\text{NH}_2$
1677	$F \text{---} \text{C}_6H_4 \text{---} CH_2 \text{---}$	2	2	1	-	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6H_3(\text{Br})\text{NH}_2$
1678	$F \text{---} \text{C}_6H_4 \text{---} CH_2 \text{---}$	2	2	1	-	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6H_3(\text{I})\text{NH}_2$
1679	$F \text{---} \text{C}_6H_4 \text{---} CH_2 \text{---}$	2	2	1	-	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6H_3(\text{Cl})\text{NH}_2$
1680	$F \text{---} \text{C}_6H_4 \text{---} CH_2 \text{---}$	2	2	1	-	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6H_3(\text{OCF}_3)\text{NH}_2$
1681	$F \text{---} \text{C}_6H_4 \text{---} CH_2 \text{---}$	2	2	1	-	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6H_3(\text{CF}_3)\text{NH}_2$
1682	$F \text{---} \text{C}_6H_4 \text{---} CH_2 \text{---}$	2	2	1	-	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6H_3(\text{Br})(\text{Cl})$
1683	$\text{C}_6H_5\text{NH}-\text{C}(=\text{O})-\text{C}_6H_4 \text{---} CH_2 \text{---}$	2	2	1	-	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_5H_2(\text{Br})_2\text{O}$

Table 1.154

5 10 15 20 25 30 35 40 45 50 55	Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_l -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
	1684		2	2	1	-	H	
	1685		2	2	1	-	H	
	1686		2	2	1	-	H	
	1687		2	2	1	-	H	
	1688		2	2	1	-	H	
	1689		2	2	1	-	H	
	1690		2	2	1	-	H	
	1691		2	2	1	-	H	
	1692		1	2	0	R	H	
	1693		1	2	0	R	H	
	1694		1	2	0	R	H	

Table 1.155

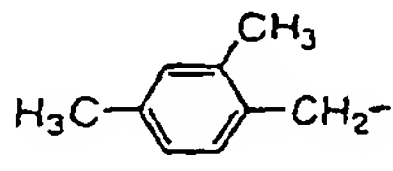
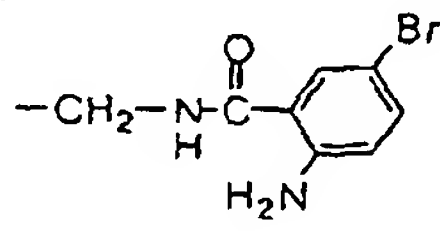
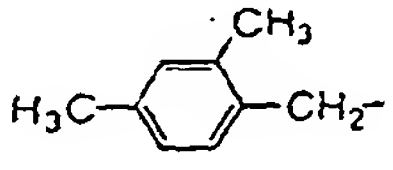
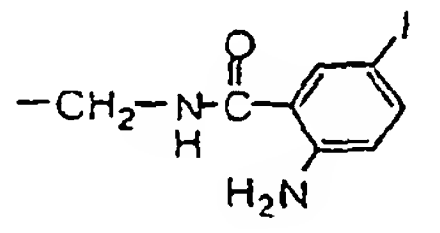
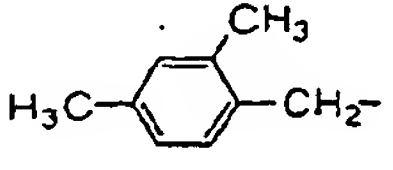
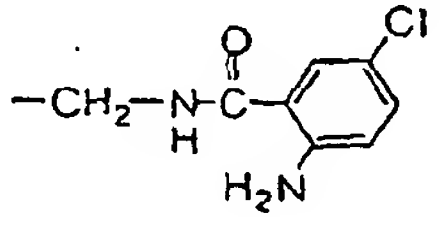
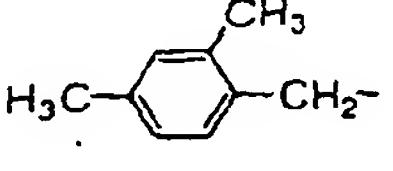
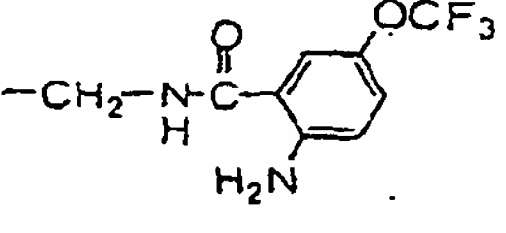
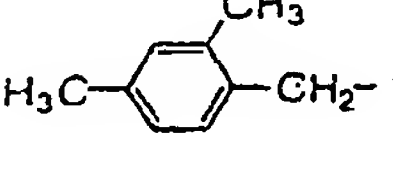
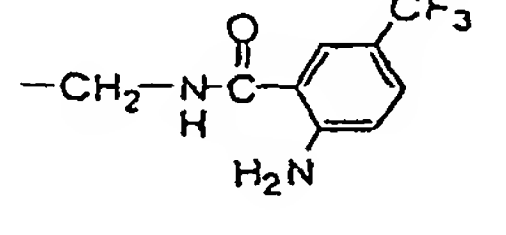
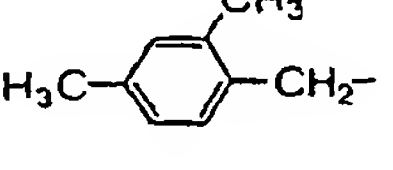
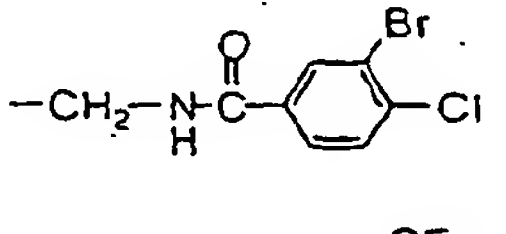
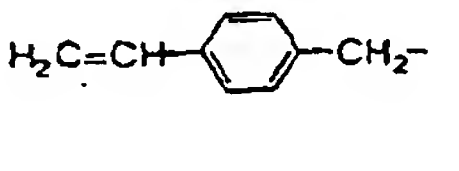
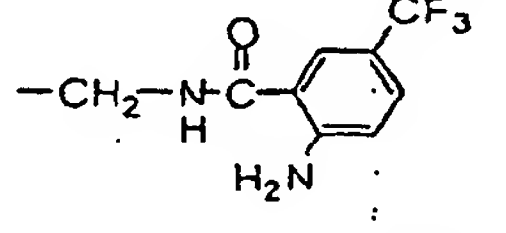
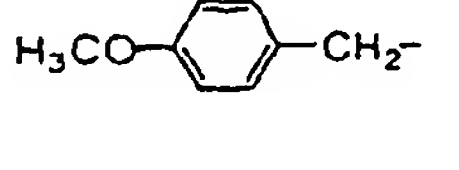
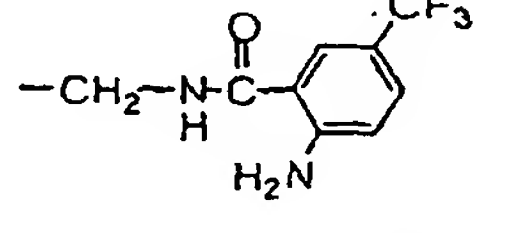
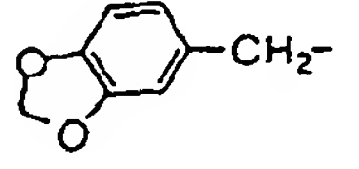
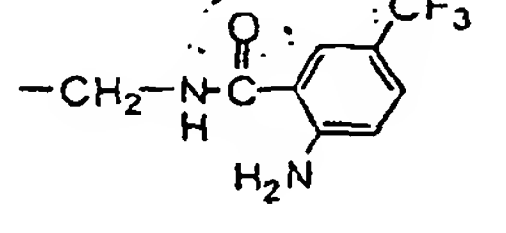
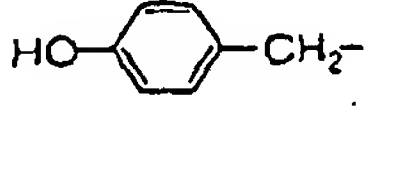
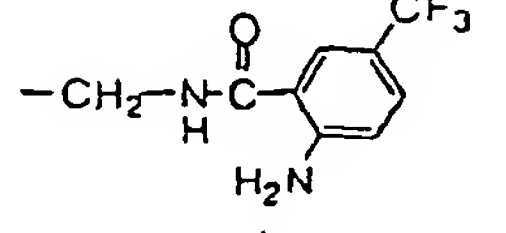
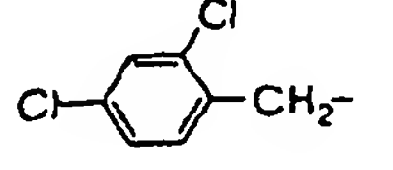
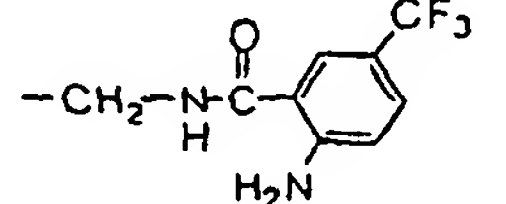
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_k -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1695		1	2	0	R	H	
1696		1	2	0	R	H	
1697		1	2	0	R	H	
1698		1	2	0	R	H	
1699		1	2	0	R	H	
1700		1	2	0	R	H	
1701		1	2	0	R	H	
1702		1	2	0	R	H	
1703		1	2	0	R	H	
1704		1	2	0	R	H	
1705		1	2	0	R	H	

Table 1.156

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1706		1	2	0	R	H	
1707		1	2	0	R	H	
1708		1	2	0	R	H	
1709		1	2	0	R	H	
1710		1	2	0	R	H	
1711		1	2	0	R	H	
1712		1	2	0	R	H	
1713		1	2	0	R	H	
1714		1	2	0	R	H	
1715		1	2	0	R	H	
1716		1	2	0	R	H	

Table 1.157

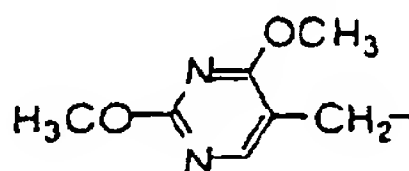
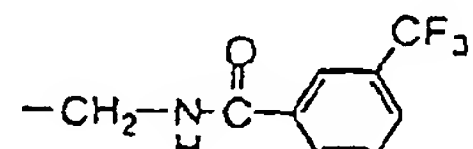
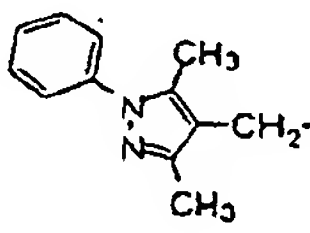
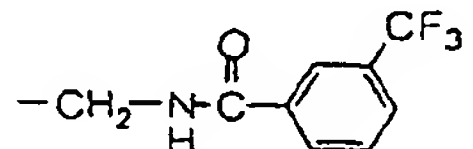
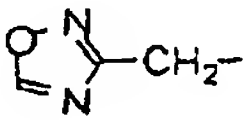
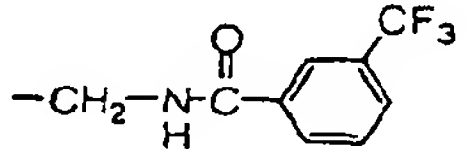
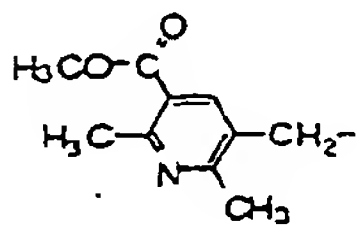
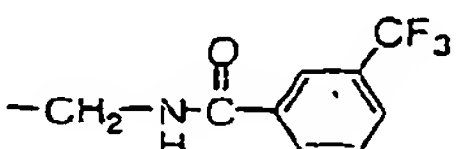
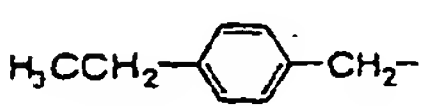
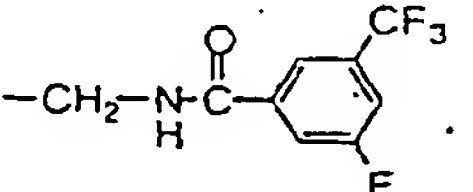
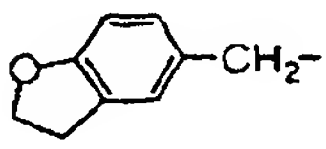
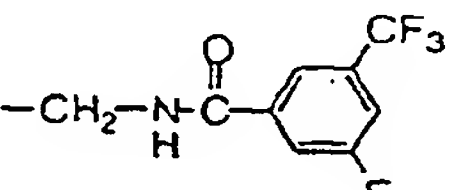
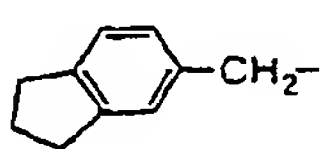
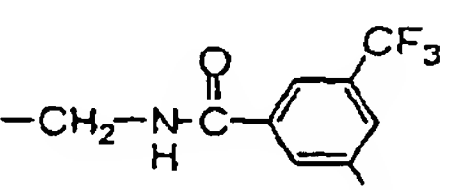
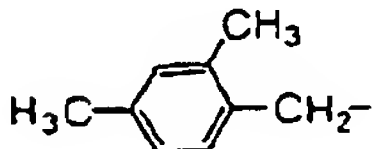
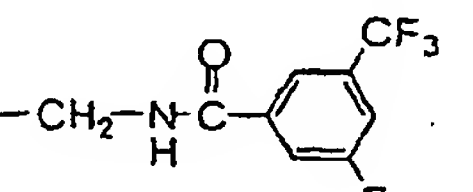
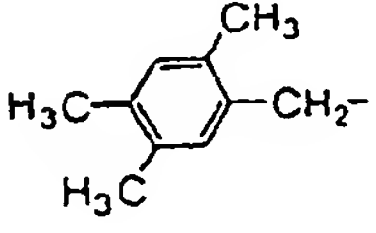
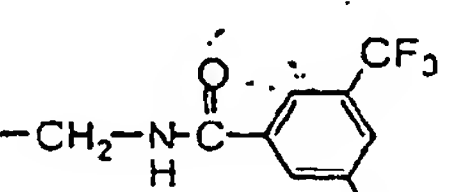
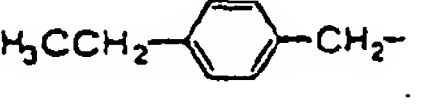
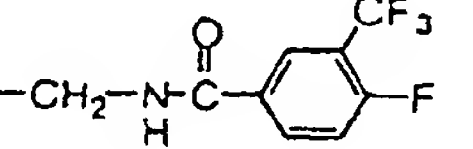
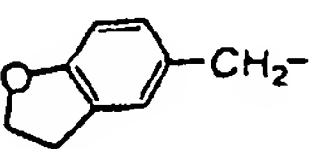
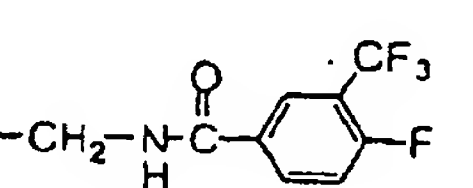
Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ R^2 \end{matrix} (CH_2)_i -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
1717		1	2	0	R	H	
1718		1	2	0	R	H	
1719		1	2	0	R	H	
1720		1	2	0	R	H	
1721		1	2	0	R	H	
1722		1	2	0	R	H	
1723		1	2	0	R	H	
1724		1	2	0	R	H	
1725		1	2	0	R	H	
1726		1	2	0	R	H	
1727		1	2	0	R	H	

Table 1.158

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_i -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1728		1	2	0	R	H	
1729		1	2	0	R	H	
1730		1	2	0	R	H	
1731		1	2	0	R	H	
1732		1	2	0	R	H	
1733		1	2	0	R	H	
1734		1	2	0	R	H	
1735		1	2	0	R	H	
1736		1	2	0	R	H	
1737		1	2	0	R	H	
1738		1	2	0	R	H	

Table 1.159

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_k \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1739	$(H_3C)_2CH - \text{C}_6H_4 - CH_2 -$	1	2	0	R	H	$-CH_2 - NH - C(=O) - \text{C}_6H_2(F)_2(CF_3) -$
1740	$\text{C}_{10}H_7 - CH_2 -$	1	2	0	R	H	$-CH_2 - NH - C(=O) - \text{C}_6H_4(Br) -$
1741	$H_3CS - \text{C}_6H_4 - CH_2 -$	1	2	0	R	H	$-CH_2 - NH - C(=O) - \text{C}_6H_4(Br) -$
1742	$H_3CCH_2 - \text{C}_6H_4 - CH_2 -$	1	2	0	R	H	$-CH_2 - NH - C(=O) - \text{C}_6H_4(Br) -$
1743	$\text{C}_{10}H_7O - CH_2 -$	1	2	0	R	H	$-CH_2 - NH - C(=O) - \text{C}_6H_4(Br) -$
1744	$H_3C - \text{C}_6H_3(CH_3) - CH_2 -$	1	2	0	R	H	$-CH_2 - NH - C(=O) - \text{C}_6H_4(Br) -$
1745	$H_3C - \text{C}_6H_3(CH_3)_2 - CH_2 -$	1	2	0	R	H	$-CH_2 - NH - C(=O) - \text{C}_6H_4(Br) -$
1746	$(H_3C)_2CH - \text{C}_6H_4 - CH_2 -$	1	2	0	R	H	$-CH_2 - NH - C(=O) - \text{C}_6H_4(Br) -$
1747	$\text{C}_{10}H_7 - CH_2 -$	1	2	0	R	H	$-CH_2 - NH - C(=O) - \text{C}_6H_3(NH_2)(Br) -$
1748	$H_3CCH_2 - \text{C}_6H_4 - CH_2 -$	1	2	0	R	H	$-CH_2 - NH - C(=O) - \text{C}_6H_3(NH_2)(Br) -$
1749	$H_3C - \text{C}_6H_3(CH_3) - CH_2 -$	1	2	0	R	H	$-CH_2 - NH - C(=O) - \text{C}_6H_3(NH_2)(Br) -$

Table 1.160

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_l -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1750		1	2	0	R	H	
1751		1	2	0	R	H	
1752		1	2	0	R	H	
1753		1	2	0	R	H	
1754		1	2	0	R	H	
1755		1	2	0	R	H	
1756		1	2	0	R	H	
1757		1	2	0	R	H	
1758		1	2	0	R	H	
1759		1	2	0	R	H	
1760		1	2	0	R	H	

Table 1.161

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1761		1	2	0	R	H	
1762		1	2	0	R	H	
1763		2	2	0	-	H	
1764		2	2	0	-	H	
1765		2	2	0	-	H	
1766		2	2	0	-	H	
1767		1	3	1	-	H	
1768		1	3	1	-	H	
1769		1	2	0	R	H	
1770		1	2	0	R	H	
1771		1	2	0	R	H	

Table 1.162

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1772		1	2	0	R	H	
1773		1	2	0	R	H	
1774		1	2	0	R	H	
1775		1	2	0	R	H	
1776		1	2	0	R	H	
1777		2	2	1	-	H	
1778		2	2	1	-	H	
1779		2	2	1	-	H	
1780		2	2	1	-	H	
1781		2	2	1	-	H	
1782		2	2	1	-	H	

Table 1.163

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_i \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1783		2	2	1	-	H	
1784		2	2	1	-	H	
1785		2	2	1	-	H	
1786		2	2	1	-	H	
1787		1	2	0	R	H	
1788		2	2	1	-	H	
1789		2	2	1	-	H	
1790		1	2	0	S	H	
1791		1	2	0	S	H	
1792		2	2	1	-	H	
1793		2	2	1	-	H	

Table 1.164

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_k \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1794		2	2	1	-	H	
1795		2	2	1	-	H	
1796		2	2	1	-	H	
1797		2	2	1	-	H	
1798		2	2	1	-	H	
1799		2	2	1	-	H	
1800		2	2	1	-	H	
1801		2	2	1	-	H	
1802		1	2	0	R	H	
1803		1	2	0	R	H	
1804		2	2	1	-	H	

Table 1.165

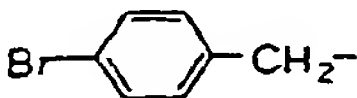
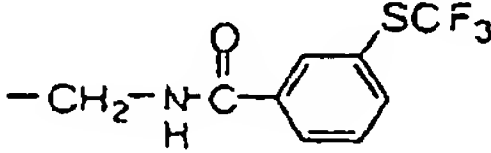

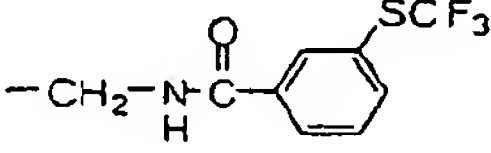
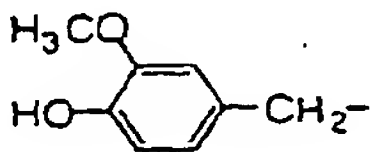
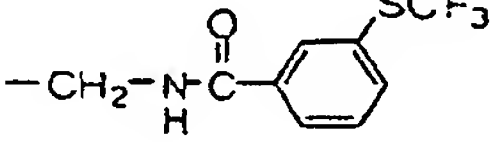
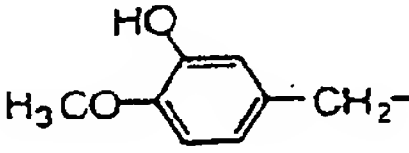
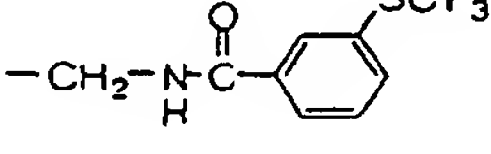
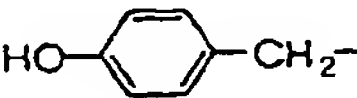
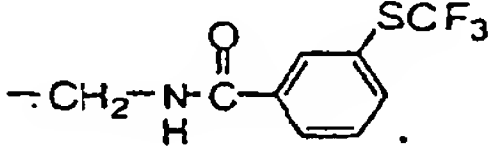
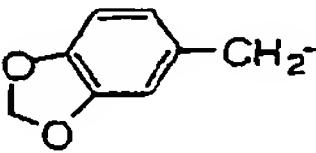
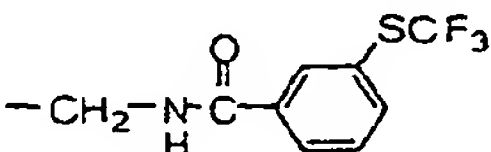
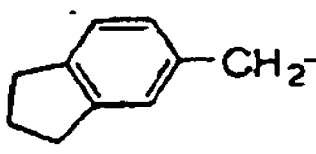
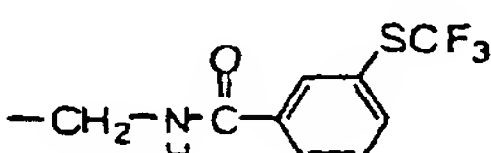

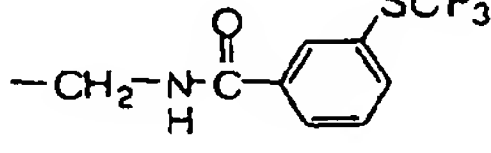
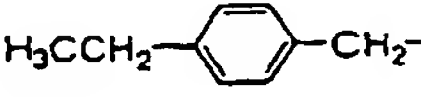
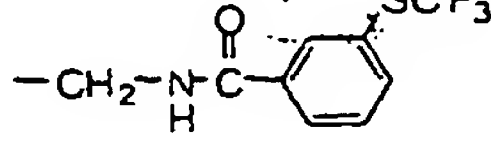
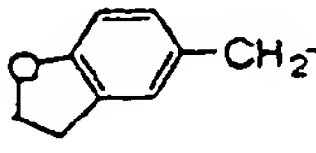
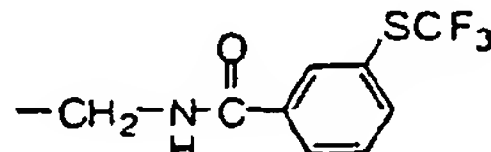
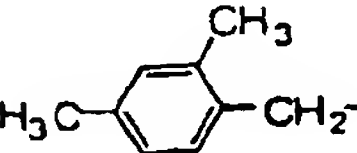
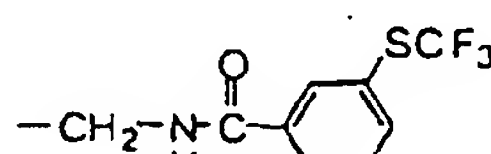
Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ R^2 \end{matrix} (CH_2)_i -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
1805		1	2	0	R	H	
1806		1	2	0	R	H	
1807		1	2	0	R	H	
1808		1	2	0	R	H	
1809		1	2	0	R	H	
1810		1	2	0	R	H	
1811		1	2	0	R	H	
1812		1	2	0	R	H	
1813		1	2	0	R	H	
1814		1	2	0	R	H	
1815		1	2	0	R	H	

Table 1.166

Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (CH_2)_j \text{---}$	k	m	n	chirality	R^3	$-(CH_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} \text{---} (CH_2)_q \text{---} G \text{---} R^6$
1816	$(CH_3)_2CH \text{---} \text{C}_6\text{H}_4 \text{---} CH_2 \text{---}$	1	2	0	R	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{SCF}_3$
1817	$(CH_3)_3C \text{---} \text{C}_6\text{H}_4 \text{---} CH_2 \text{---}$	1	2	0	R	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{SCF}_3$
1818	$Br \text{---} \text{C}_6\text{H}_4 \text{---} CH_2 \text{---}$	1	2	0	R	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{OCHF}_2$
1819	$H_3CO \text{---} \text{C}_6\text{H}_4 \text{---} CH_2 \text{---}$	1	2	0	R	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{OCHF}_2$
1820	$\begin{matrix} H_3CO \\ HO \end{matrix} \text{---} \text{C}_6\text{H}_3 \text{---} CH_2 \text{---}$	1	2	0	R	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_3-\text{OCHF}_2$
1821	$\begin{matrix} HO \\ H_3CO \end{matrix} \text{---} \text{C}_6\text{H}_3 \text{---} CH_2 \text{---}$	1	2	0	R	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_3-\text{OCHF}_2$
1822	$HO \text{---} \text{C}_6\text{H}_4 \text{---} CH_2 \text{---}$	1	2	0	R	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{OCHF}_2$
1823	$\text{C}_6\text{H}_3 \text{---} CH_2 \text{---}$	1	2	0	R	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_3-\text{OCHF}_2$
1824	$\text{C}_{10}\text{H}_7 \text{---} CH_2 \text{---}$	1	2	0	R	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{OCHF}_2$
1825	$H_3CS \text{---} \text{C}_6\text{H}_4 \text{---} CH_2 \text{---}$	1	2	0	R	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{OCHF}_2$
1826	$H_3CCH_2 \text{---} \text{C}_6\text{H}_4 \text{---} CH_2 \text{---}$	1	2	0	R	H	$-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{OCHF}_2$

Table 1.167

Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ R^2 \end{matrix} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
1827		1	2	0	R	H	
1828		1	2	0	R	H	
1829		1	2	0	R	H	
1830		1	2	0	R	H	
1831		1	2	0	R	H	
1832		1	2	0	R	H	
1833		1	2	0	R	H	
1834		1	2	0	R	H	
1835		1	2	0	R	H	
1836		1	2	0	R	H	
1837		1	2	0	R	H	

Table 1.168

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_i \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1838		1	2	0	R	H	
1839		1	2	0	R	H	
1840		1	2	0	R	H	
1841		1	2	0	R	H	
1842		1	2	0	R	H	
1843		1	2	0	R	H	
1844		1	2	0	R	H	
1845		1	2	0	R	H	
1846		1	2	0	R	H	
1847		1	2	0	R	H	
1848		1	2	0	R	H	

Table 1.169

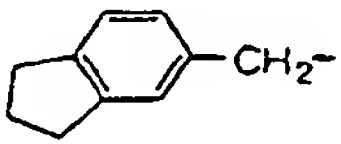
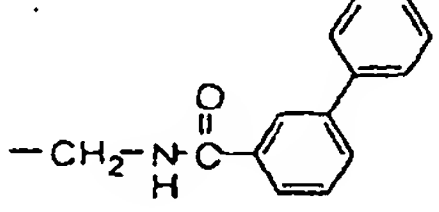
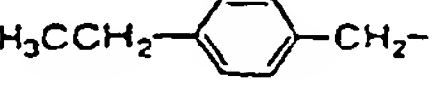
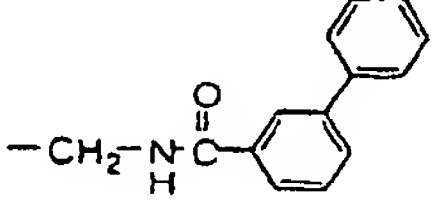
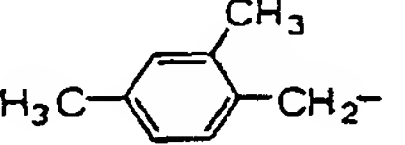
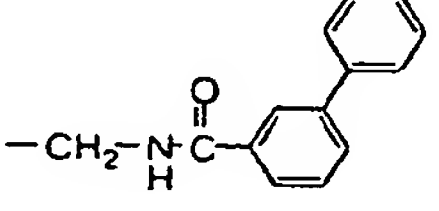
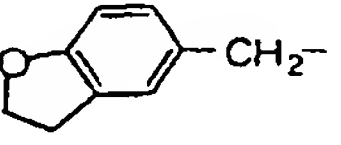
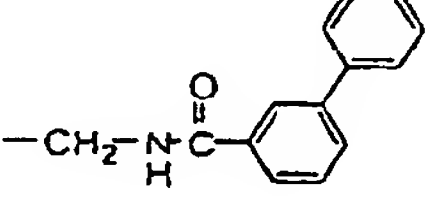
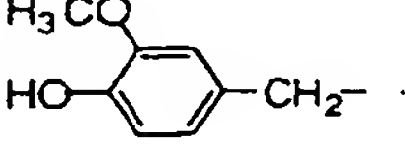
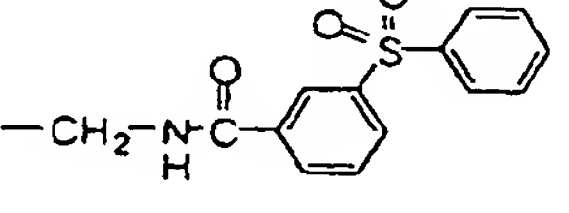
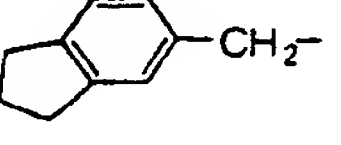
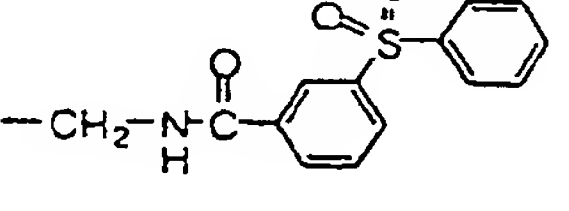

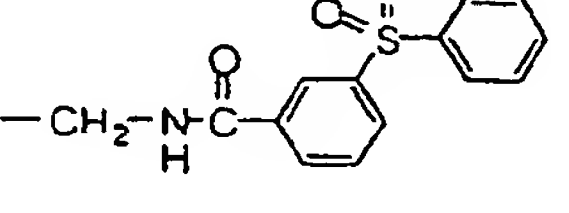
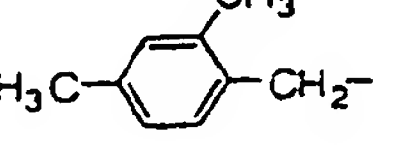
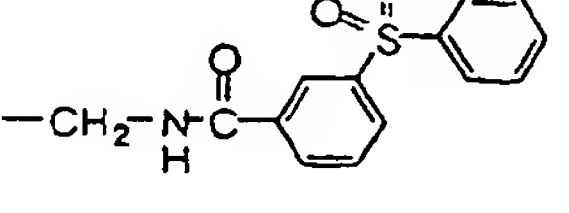
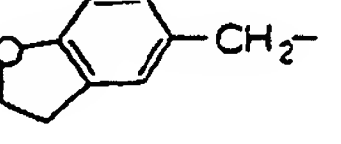
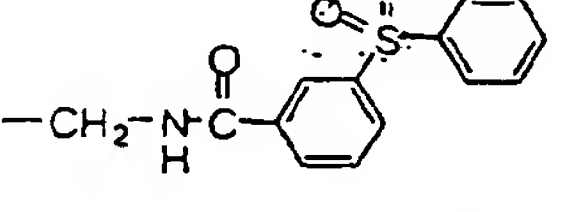
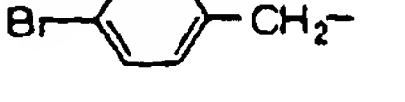
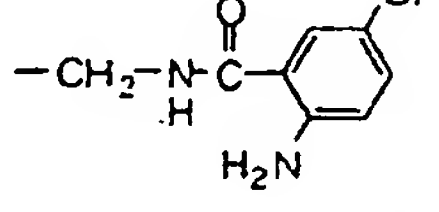
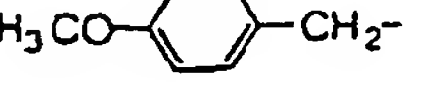
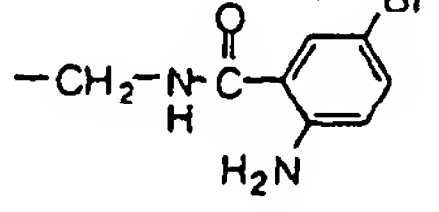
Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ R^2 \end{matrix} (CH_2)_i -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
1849		1	2	0	R	H	
1850		1	2	0	R	H	
1851		1	2	0	R	H	
1852		1	2	0	R	H	
1853		1	2	0	R	H	
1854		1	2	0	R	H	
1855		1	2	0	R	H	
1856		1	2	0	R	H	
1857		1	2	0	R	H	
1858		1	2	0	R	H	
1859		1	2	0	R	H	

Table 1.170

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1860		1	2	0	R	H	
1861		1	2	0	R	H	
1862		1	2	0	R	H	
1863		1	2	0	R	H	
1864		1	2	0	R	H	
1865		1	2	0	R	H	
1866		1	2	0	R	H	
1867		1	2	0	R	H	
1868		1	2	0	R	H	
1869		1	2	0	R	H	
1870		1	2	0	R	H	

Table 1.171

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_i -$	k	m	n	chirality	R ³	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1871	$\begin{array}{c} H_3CO \\ \\ HO - \text{C}_6H_4 - CH_2 - \end{array}$	1	2	0	R	H	$-CH_2 - \begin{array}{c} H \\ \\ N - C(=O) - \text{C}_6H_3(I) - NH_2 \end{array}$
1872	$\begin{array}{c} HO \\ \\ H_3CO - \text{C}_6H_4 - CH_2 - \end{array}$	1	2	0	R	H	$-CH_2 - \begin{array}{c} H \\ \\ N - C(=O) - \text{C}_6H_3(I) - NH_2 \end{array}$
1873	$HO - \text{C}_6H_4 - CH_2 -$	1	2	0	R	H	$-CH_2 - \begin{array}{c} H \\ \\ N - C(=O) - \text{C}_6H_3(I) - NH_2 \end{array}$
1874	$\begin{array}{c} \text{C}_6H_3(OCH_2)_2 - CH_2 - \end{array}$	1	2	0	R	H	$-CH_2 - \begin{array}{c} H \\ \\ N - C(=O) - \text{C}_6H_3(I) - NH_2 \end{array}$
1875	$\begin{array}{c} \text{C}_6H_3(\text{cyclopentyl})_2 - CH_2 - \end{array}$	1	2	0	R	H	$-CH_2 - \begin{array}{c} H \\ \\ N - C(=O) - \text{C}_6H_3(I) - NH_2 \end{array}$
1876	$H_3CS - \text{C}_6H_4 - CH_2 -$	1	2	0	R	H	$-CH_2 - \begin{array}{c} H \\ \\ N - C(=O) - \text{C}_6H_3(I) - NH_2 \end{array}$
1877	$H_3CCH_2 - \text{C}_6H_4 - CH_2 -$	1	2	0	R	H	$-CH_2 - \begin{array}{c} H \\ \\ N - C(=O) - \text{C}_6H_3(I) - NH_2 \end{array}$
1878	$\begin{array}{c} \text{C}_6H_3(\text{cyclopentyl})_2 - CH_2 - \end{array}$	1	2	0	R	H	$-CH_2 - \begin{array}{c} H \\ \\ N - C(=O) - \text{C}_6H_3(I) - NH_2 \end{array}$
1879	$\begin{array}{c} CH_3 \\ \\ H_3C - \text{C}_6H_3 - CH_2 - \\ \\ H_3C \end{array}$	1	2	0	R	H	$-CH_2 - \begin{array}{c} H \\ \\ N - C(=O) - \text{C}_6H_3(I) - NH_2 \end{array}$
1880	$(CH_3)_2CH - \text{C}_6H_4 - CH_2 -$	1	2	0	R	H	$-CH_2 - \begin{array}{c} H \\ \\ N - C(=O) - \text{C}_6H_3(I) - NH_2 \end{array}$
1881	$(CH_3)_3C - \text{C}_6H_4 - CH_2 -$	1	2	0	R	H	$-CH_2 - \begin{array}{c} H \\ \\ N - C(=O) - \text{C}_6H_3(I) - NH_2 \end{array}$

Table 1.172

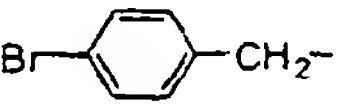
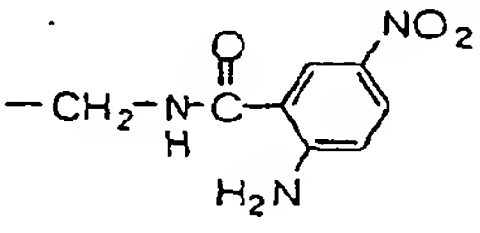
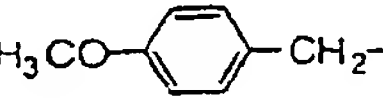
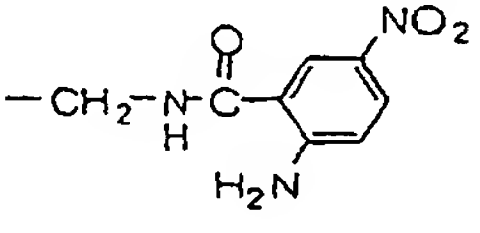
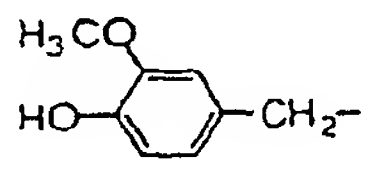
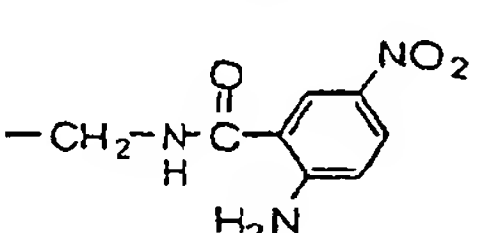
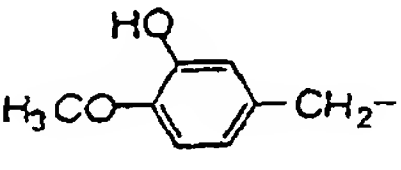
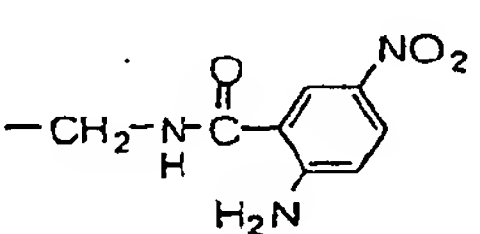
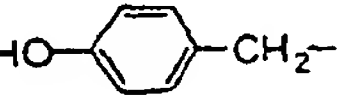
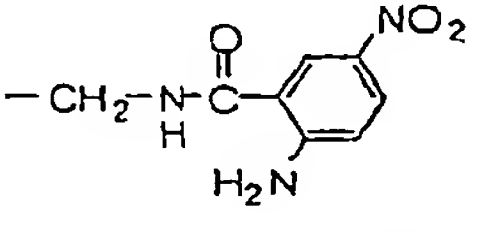
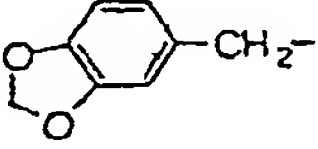
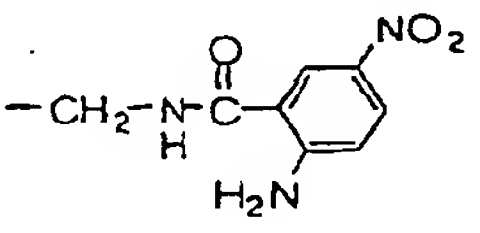
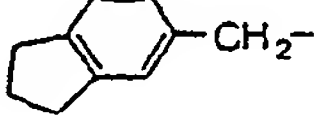
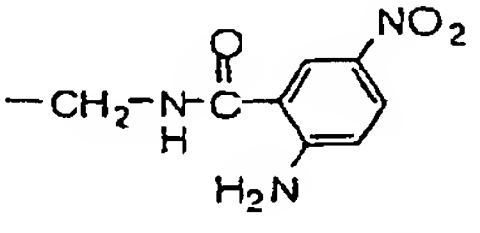

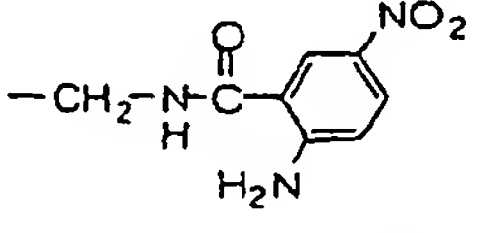
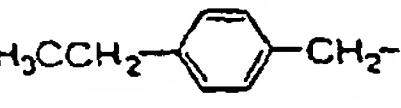
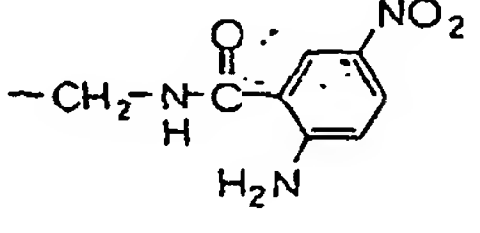
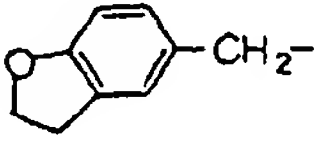
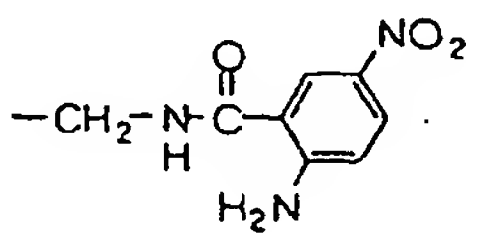
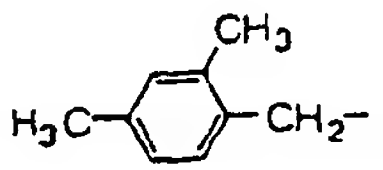
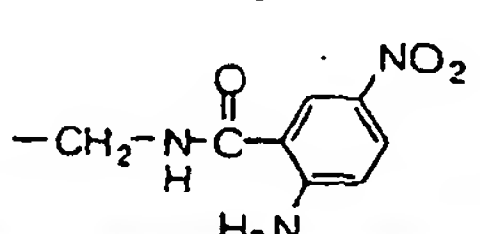
Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ R^2 \end{matrix} (CH_2)_j$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q G-R^6$
1882		1	2	0	R	H	
1883		1	2	0	R	H	
1884		1	2	0	R	H	
1885		1	2	0	R	H	
1886		1	2	0	R	H	
1887		1	2	0	R	H	
1888		1	2	0	R	H	
1889		1	2	0	R	H	
1890		1	2	0	R	H	
1891		1	2	0	R	H	
1892		1	2	0	R	H	

Table 1.173

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1893		1	2	0	R	H	
1894		1	2	0	R	H	
1895		1	2	0	R	H	
1896		1	2	0	R	H	
1897		1	2	0	R	H	
1898		1	2	0	R	H	
1899		1	2	0	R	H	
1900		1	2	0	R	H	
1901		1	2	0	R	H	
1902		1	2	0	R	H	
1903		2	2	1	-	H	

Table 1.174

5 10 15 20 25 30 35 40 45 50 55	Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_k \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
	1904	$H_3C(CH_2)_2-\text{C}_6H_4-CH_2-$	2	2	1	-	H	$-CH_2-NH-C(=O)-\text{C}_6H_3(NH_2)(OCF_3)-$
	1905	$Cl-\text{C}_6H_3(Cl)-CH_2-$	1	2	0	R	H	$-CH_2-NH-C(=O)-\text{C}_6H_3(NH_2)(OCF_3)-$
	1906	$\text{C}_6H_3(OCH_2)_2-CH_2-$	1	2	0	R	H	$-CH_2-NH-C(=O)-\text{C}_6H_3(NH_2)(OCF_3)-$
	1907	$HO-\text{C}_6H_4-CH_2-$	1	2	0	R	H	$-CH_2-NH-C(=O)-\text{C}_6H_3(NH_2)(OCF_3)-$
	1908	$H_3CO-\text{C}_6H_4-CH_2-$	1	2	0	R	H	$-CH_2-NH-C(=O)-\text{C}_6H_3(NH_2)(OCF_3)-$
	1909	$H_2C=CH-\text{C}_6H_4-CH_2-$	1	2	0	R	H	$-CH_2-NH-C(=O)-\text{C}_6H_3(NH_2)(OCF_3)-$
	1910	$Br-\text{C}_6H_4-CH_2-$	2	2	1	-	H	$-CH_2-NH-C(=O)-\text{C}_6H_3(NH_2)(OCF_3)-$
	1911	$Cl-\text{C}_6H_3(Cl)-CH_2-$	2	2	1	-	H	$-CH_2-NH-C(=O)-\text{C}_6H_3(NH_2)(OCF_3)-$
	1912	$HO-\text{C}_6H_4-CH_2-$	2	2	1	-	H	$-CH_2-NH-C(=O)-\text{C}_6H_3(NH_2)(OCF_3)-$
	1913	$H_3C-\text{C}_6H_3(CH_3)-CH_2-$	2	2	1	-	H	$-CH_2-NH-C(=O)-\text{C}_6H_3(NH_2)(OCF_3)-$
	1914	$H_3C-\text{C}_6H_4-CH_2-$	2	2	1	-	H	$-CH_2-NH-C(=O)-\text{C}_6H_3(NH_2)(OCF_3)-$

Table 1.175

Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (CH_2)_j \text{---}$	k	m	n	chirality	R^3	$-(CH_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} (CH_2)_q \text{---} G \text{---} R^6$
1915		1	2	0	R	H	
1916		1	2	0	R	H	
1917		2	2	1	-	H	
1918		2	2	1	-	H	
1919		2	2	1	-	H	
1920		2	2	1	-	H	
1921		1	2	0	R	H	
1922		2	2	1	-	H	
1923		2	2	1	-	H	
1924		2	2	1	-	H	
1925		2	2	1	-	H	

Table 1.176

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1926		2	2	1	-	H	
1927		2	2	1	-	H	
1928		2	2	1	-	H	
1929		2	2	1	-	H	
1930		2	2	1	-	H	
1931		2	2	1	-	H	
1932		2	2	1	-	H	
1933		2	2	1	-	H	
1934		2	2	1	-	H	
1935		2	2	1	-	H	
1936		2	2	1	-	H	

Table 1.177

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ -C- \\ \\ R^5 \end{array} (CH_2)_q G-R^6$
1937		2	2	1	-	H	
1938		2	2	1	-	H	
1939		2	2	1	-	H	
1940		2	2	1	-	H	
1941		2	2	1	-	H	
1942		2	2	1	-	H	
1943		2	2	1	-	H	
1944		2	2	1	-	H	
1945		2	2	1	-	H	
1946		2	2	1	-	H	
1947		2	2	1	-	H	

Table 1.178

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_i \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
1948		2	2	1	-	H	
1949		2	2	1	-	H	
1950		2	2	1	-	H	
1951		2	2	1	-	H	
1952		2	2	1	-	H	
1953		2	2	1	-	H	
1954		2	2	1	-	H	
1955		2	2	1	-	H	
1956		2	2	1	-	H	
1957		2	2	1	-	H	
1958		2	2	1	-	H	

Table 1.179

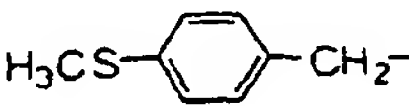
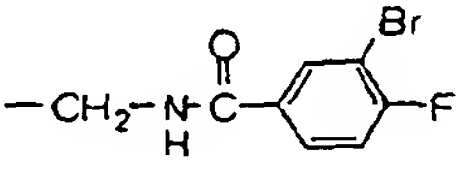
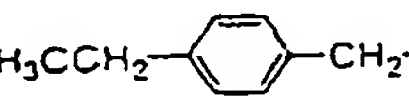
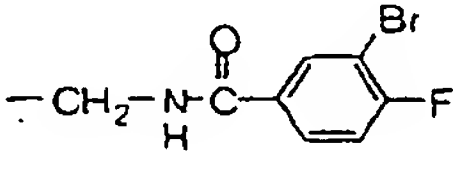
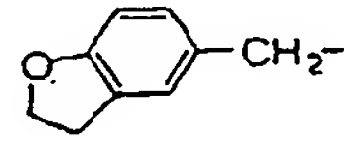
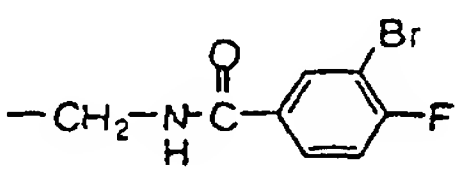
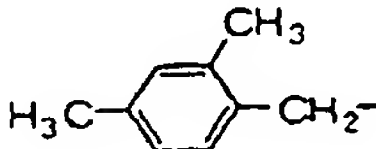
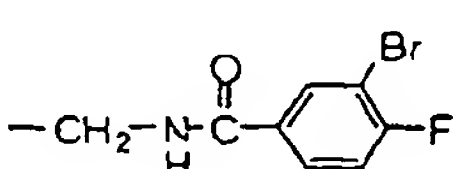
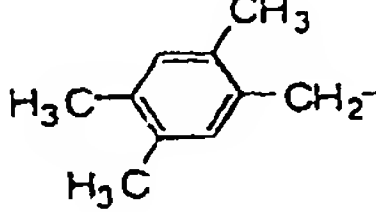
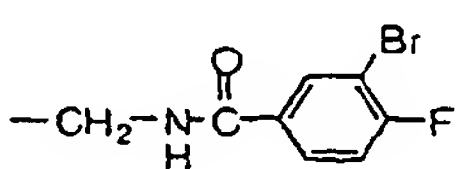

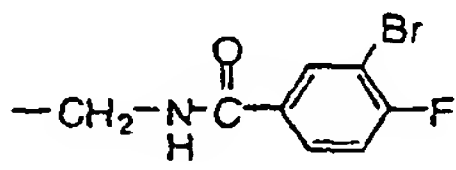

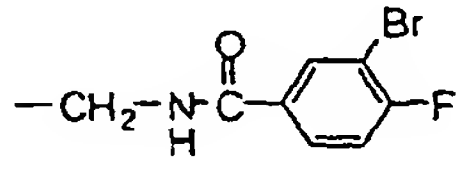
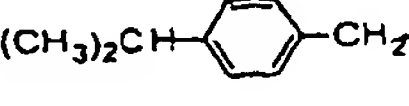
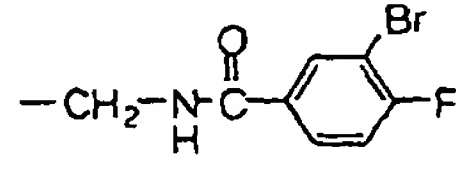
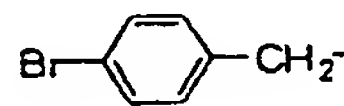
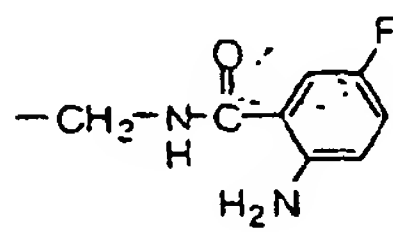
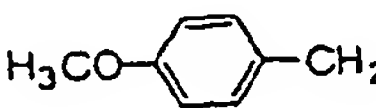
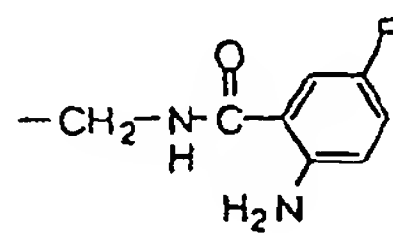

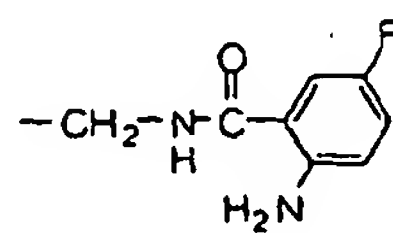
Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ R^2 \end{matrix} (CH_2)_l -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
1959		2	2	1	-	H	
1960		2	2	1	-	H	
1961		2	2	1	-	H	
1962		2	2	1	-	H	
1963		2	2	1	-	H	
1964		2	2	1	-	H	
1965		2	2	1	-	H	
1966		2	2	1	-	H	
1967		2	2	1	-	H	
1968		2	2	1	-	H	
1969		2	2	1	-	H	

Table 1.180

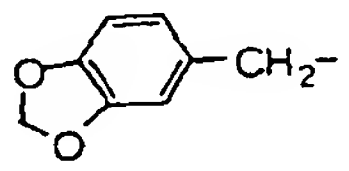
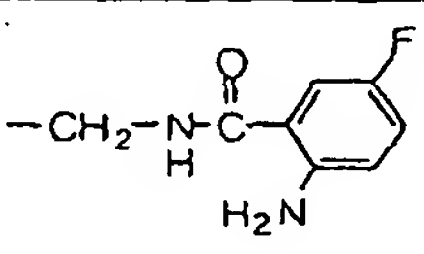
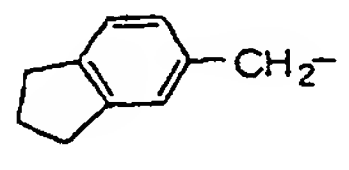
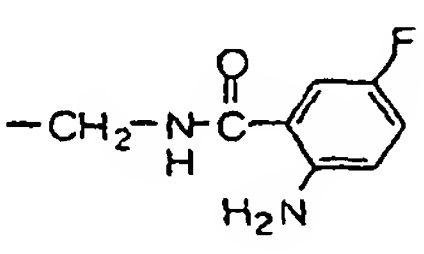
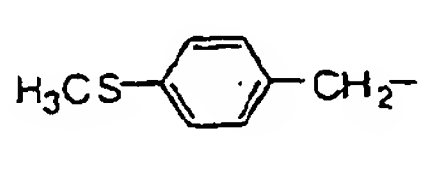
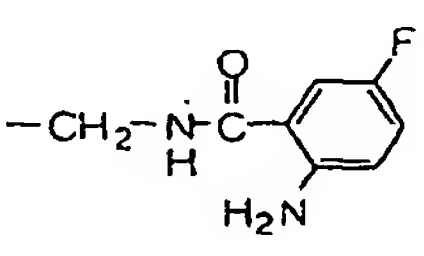
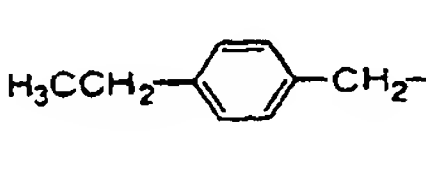
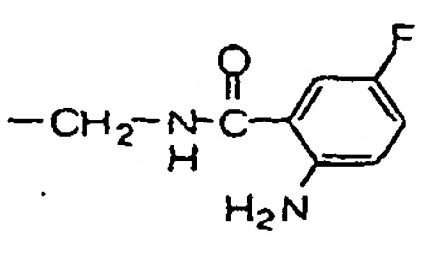
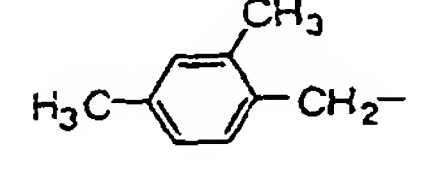
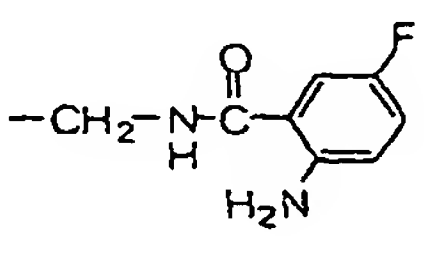
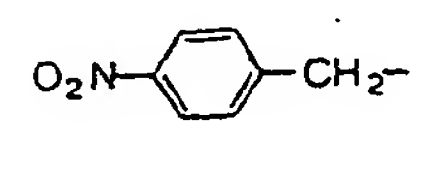
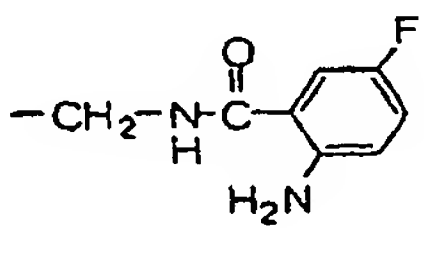
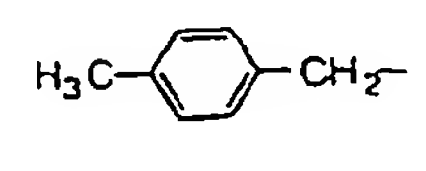
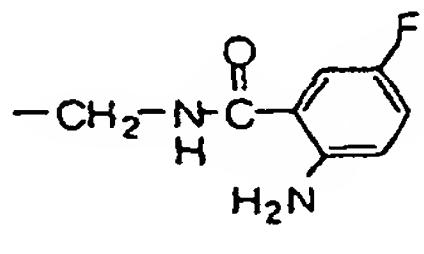
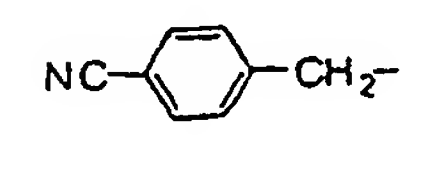
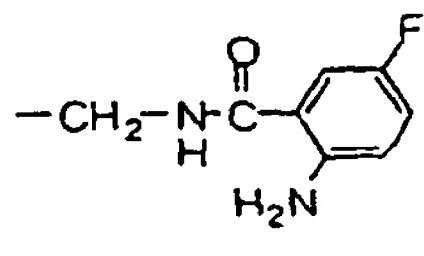
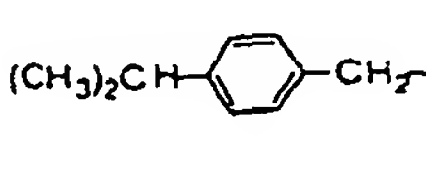
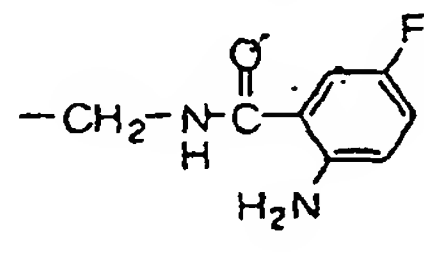
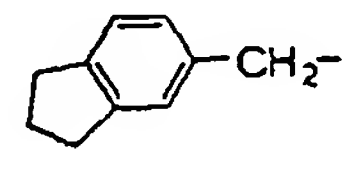
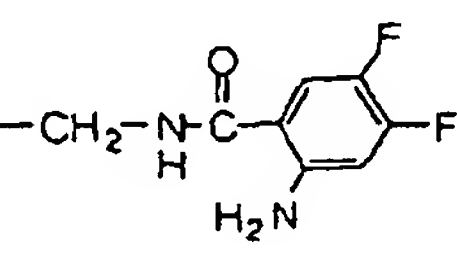
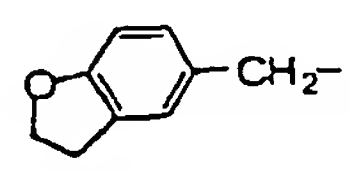
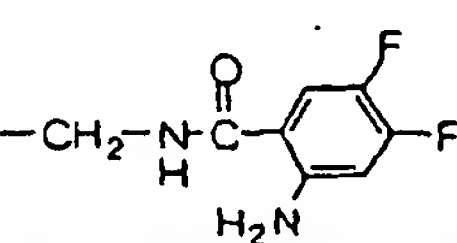
Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ R^2 \end{matrix} (CH_2)_l$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q - G - R^6$
1970		2	2	1	-	H	
1971		2	2	1	-	H	
1972		2	2	1	-	H	
1973		2	2	1	-	H	
1974		2	2	1	-	H	
1975		2	2	1	-	H	
1976		2	2	1	-	H	
1977		2	2	1	-	H	
1978		2	2	1	-	H	
1979		2	2	1	-	H	
1980		2	2	1	-	H	

Table 1.181


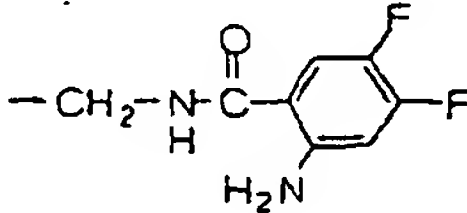
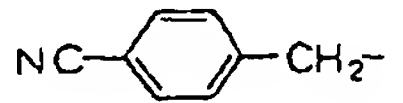
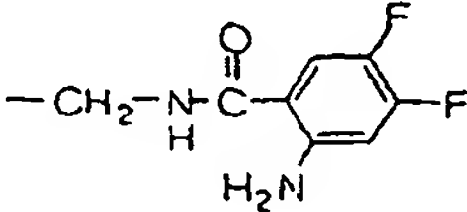
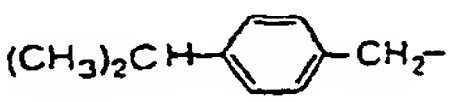
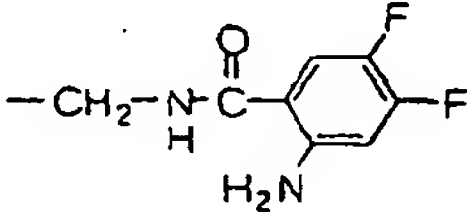
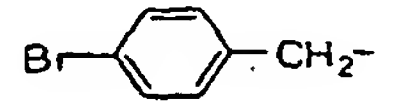
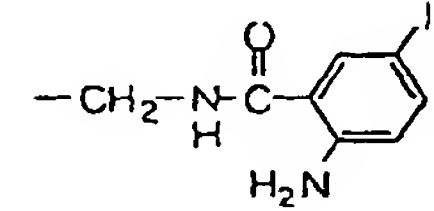

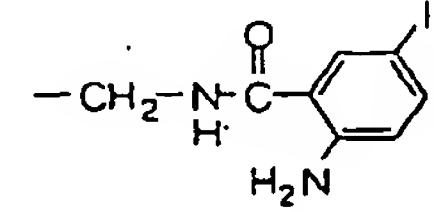
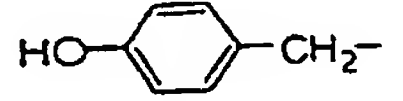
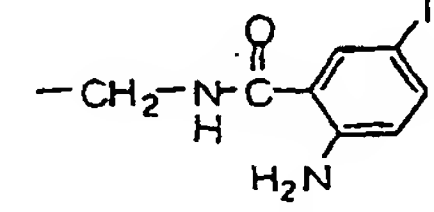
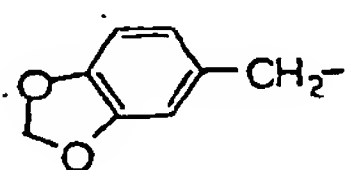
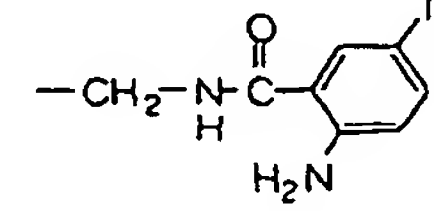
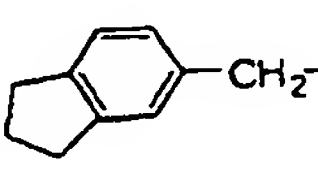
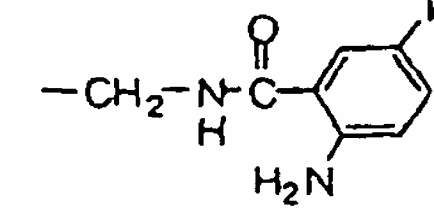

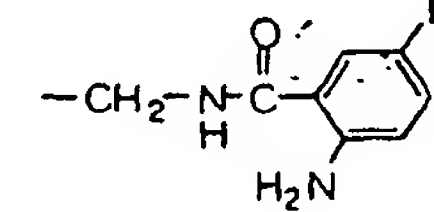
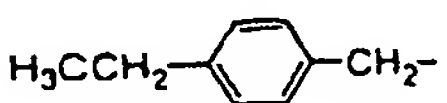
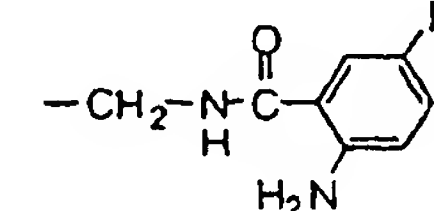
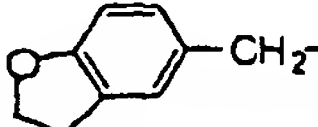
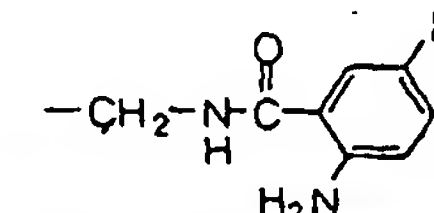
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p-\overset{\overset{R^4}{ }}{\underset{\underset{R^5}{ }}{C}}-(CH_2)_q-G-R^6$
1981		2	2	1	-	H	
1982		2	2	1	-	H	
1983		2	2	1	-	H	
1984		2	2	1	-	H	
1985		2	2	1	-	H	
1986		2	2	1	-	H	
1987		2	2	1	-	H	
1988		2	2	1	-	H	
1989		2	2	1	-	H	
1990		2	2	1	-	H	
1991		2	2	1	-	H	

Table 1.182

5 10 15 20 25 30 35 40 45 50 55	Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
	1992		2	2	1	-	H	
	1993		2	2	1	-	H	
	1994		2	2	1	-	H	
	1995		2	2	1	-	H	
	1996		2	2	1	-	H	
	1997		2	2	1	-	H	
	1998		2	2	1	-	H	
	1999		2	2	1	-	H	
	2000		2	2	1	-	H	
	2001		2	2	1	-	H	
	2002		2	2	1	-	H	

Table 1.183

5	Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
10	2003		2	2	1	-	H	
15	2004		2	2	1	-	H	
20	2005		2	2	1	-	H	
25	2006		2	2	1	-	H	
30	2007		2	2	1	-	H	
35	2008		2	2	1	-	H	
40	2009		2	2	1	-	H	
45	2010		2	2	1	-	H	
50	2011		2	2	1	-	H	
55	2012		2	2	1	-	H	
	2013		2	2	1	-	H	

Table 1.184


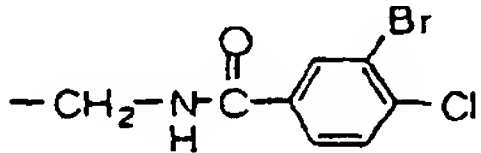
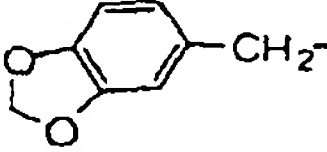
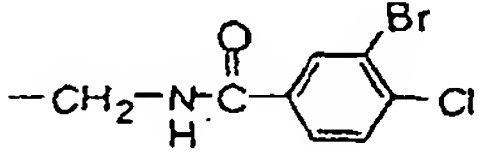
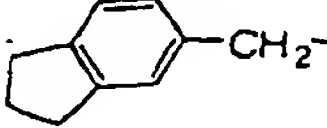
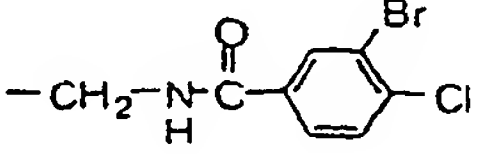

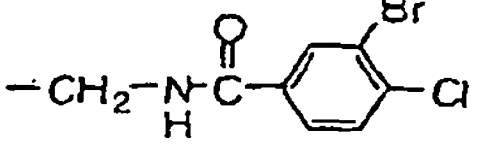
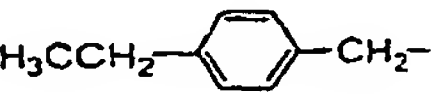
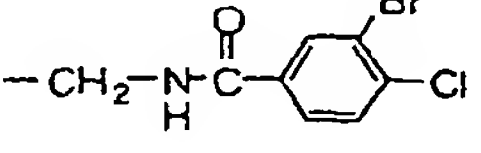
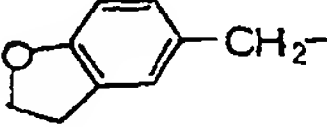
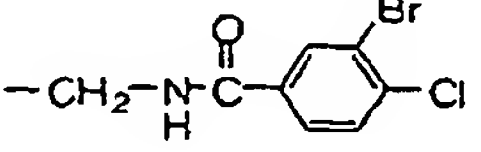
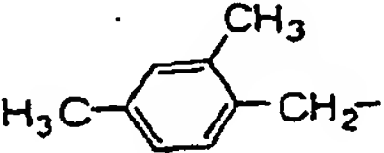
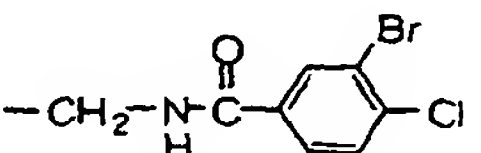

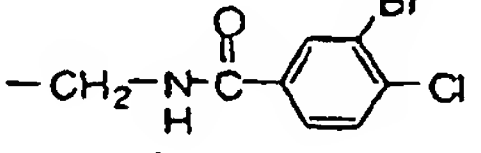
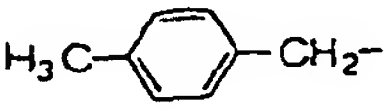
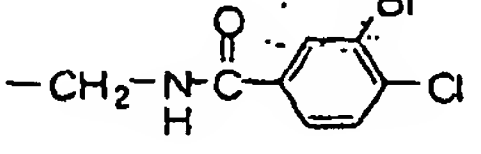
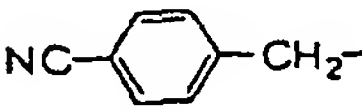
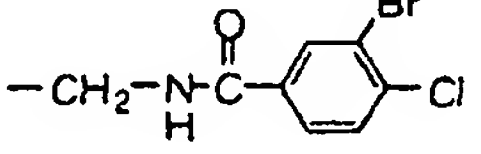
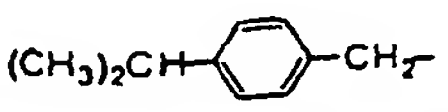
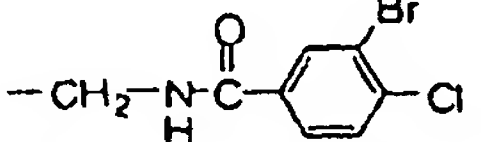
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
2014		2	2	1	-	H	
2015		2	2	1	-	H	
2016		2	2	1	-	H	
2017		2	2	1	-	H	
2018		2	2	1	-	H	
2019		2	2	1	-	H	
2020		2	2	1	-	H	
2021		2	2	1	-	H	
2022		2	2	1	-	H	
2023		2	2	1	-	H	
2024		2	2	1	-	H	

Table 1.185

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_l$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
2025		2	2	1	-	H	
2026		2	2	1	-	H	
2027		2	2	1	-	H	
2028		2	2	1	-	H	
2029		2	2	1	-	H	
2030		2	2	1	-	H	
2031		2	2	1	-	H	
2032		2	2	1	-	H	
2033		2	2	1	-	H	
2034		2	2	1	-	H	
2035		2	2	1	-	H	

Table 1.186

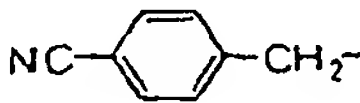
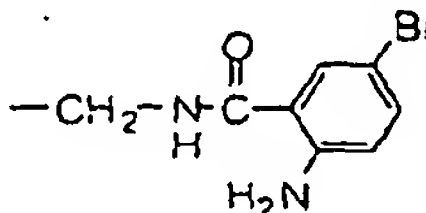
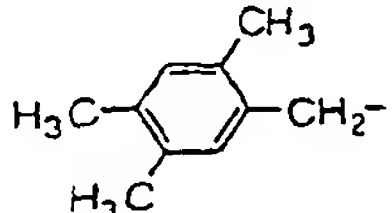
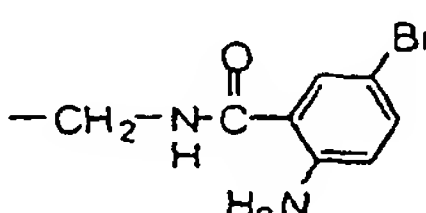
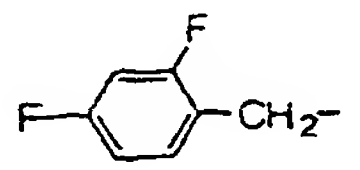
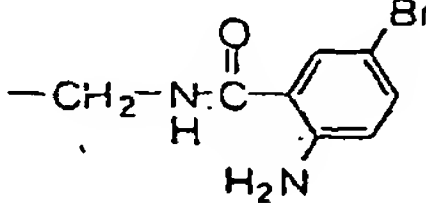

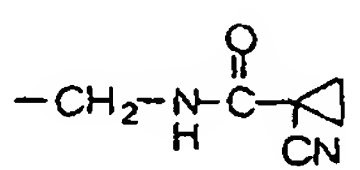
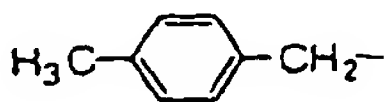
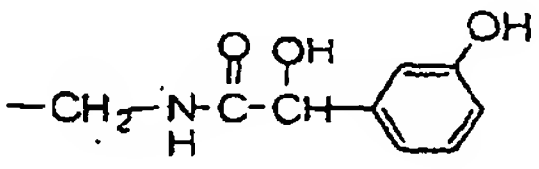

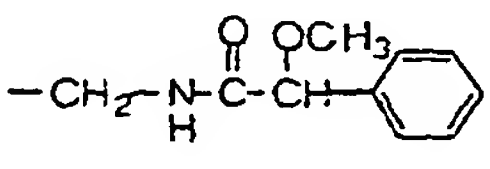
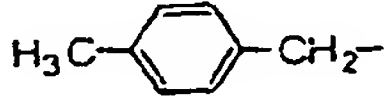
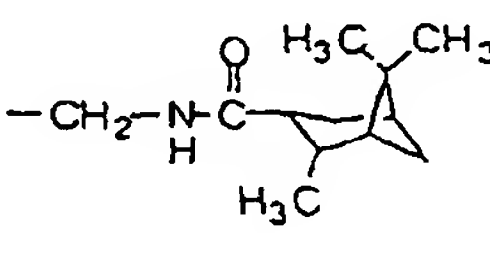
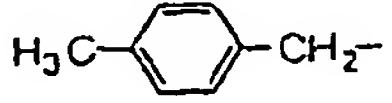
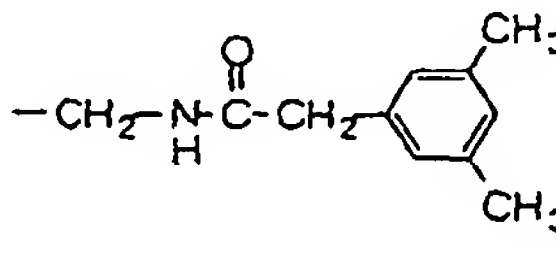
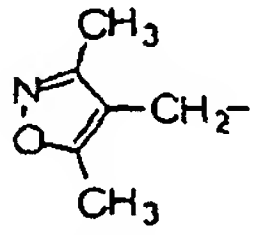
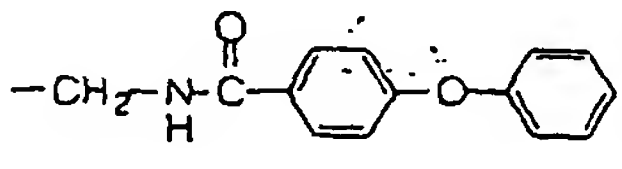
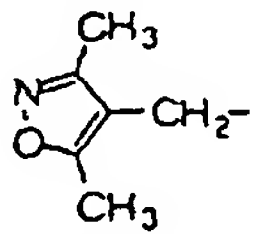
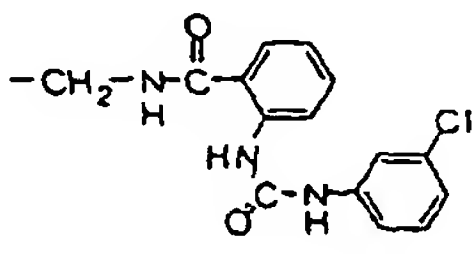
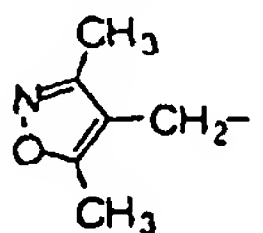
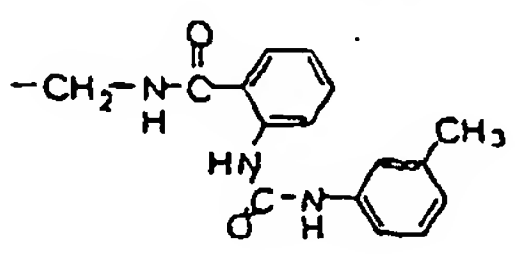
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_l \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
2036		2	2	1	-	H	
2037		2	2	1	-	H	
2038		2	2	1	-	H	
2039		2	2	1	-	H	
2040		1	2	0	R	H	
2041		1	2	0	R	H	
2042		1	2	0	R	H	
2043		1	2	0	R	H	
2044		1	2	0	R	H	
2045		1	2	0	R	H	
2046		1	2	0	R	H	

Table 1.187

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_i \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
2047		1	2	0	R	H	
2048		1	2	0	R	H	
2049		1	2	0	R	H	
2050		1	2	0	R	H	
2051		1	2	0	R	H	
2052		2	2	1	-	H	
2053		2	2	1	-	H	
2054		2	2	1	-	H	
2055		2	2	1	-	H	
2056		2	2	1	-	H	
2057		2	2	1	-	H	

Table 1.188

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
2058		2	2	1	-	H	
2059		2	2	1	-	H	
2060		2	2	1	-	H	
2061		2	2	1	-	H	
2062		2	2	1	-	H	
2063		2	2	1	-	H	
2064		2	2	1	-	H	
2065		2	2	1	-	H	
2066		2	2	1	-	H	
2067		2	2	1	-	H	
2068		2	2	1	-	H	

Table 1.189

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q G-R^6$
2069		2	2	1	-	H	
2070		2	2	1	-	H	
2071		2	2	1	-	H	
2072		2	2	1	-	H	
2073		2	2	1	-	H	
2074		2	2	1	-	H	
2075		2	2	1	-	H	
2076		2	2	1	-	H	
2077		2	2	1	-	H	
2078		2	2	1	-	H	
2079		2	2	1	-	H	

Table 1.190

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_i \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ (CH_2)_q - G - R^6 \\ \\ R^5 \end{array}$
2080		2	2	1	-	H	
2081		2	2	1	-	H	
2082		2	2	1	-	H	
2083		1	2	0	R	H	
2084		1	2	0	R	H	
2085		1	2	0	R	H	
2086		1	2	0	R	H	
2087		1	2	0	R	H	
2088		1	2	0	R	H	
2089		1	2	0	R	H	
2090		1	2	0	R	H	

Table 1.191

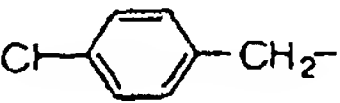
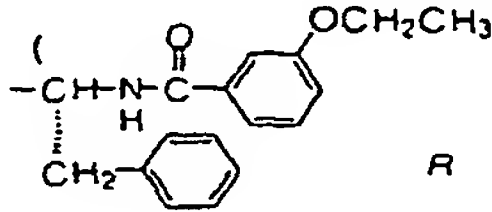
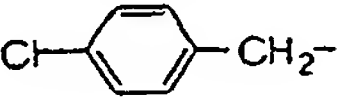
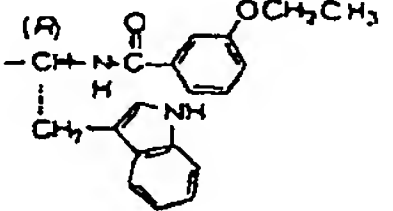
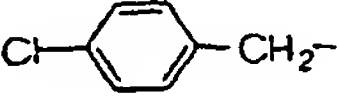
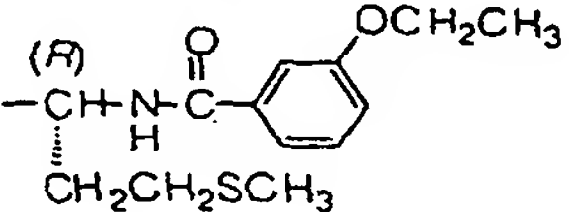
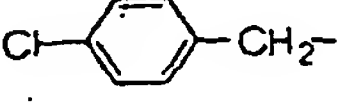
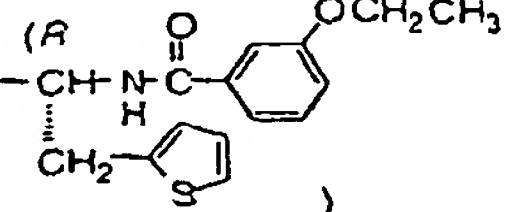
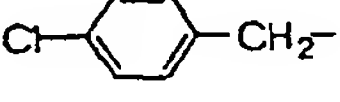
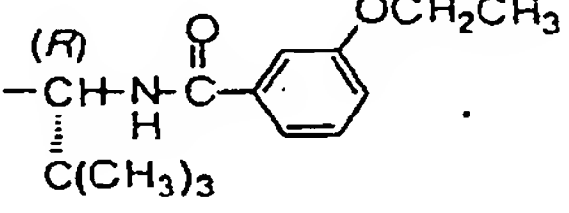
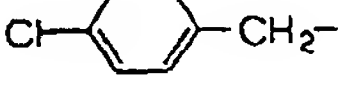
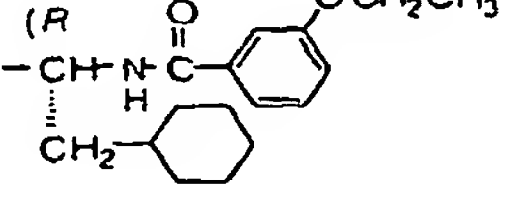
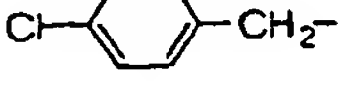
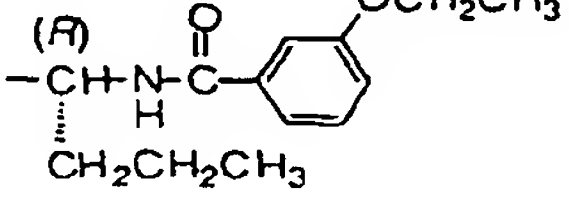
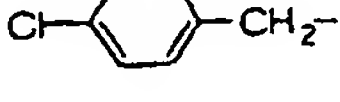
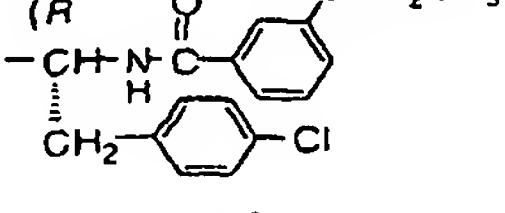
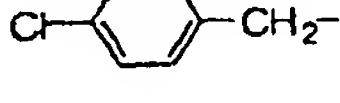
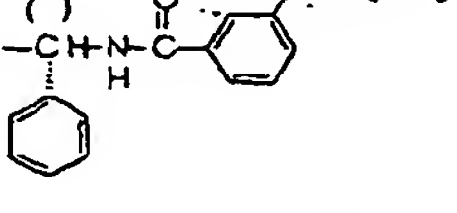
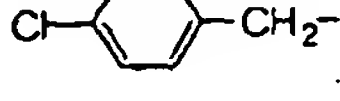
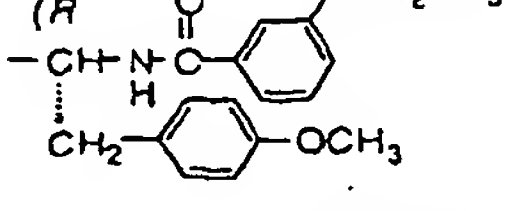
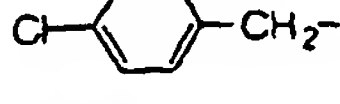
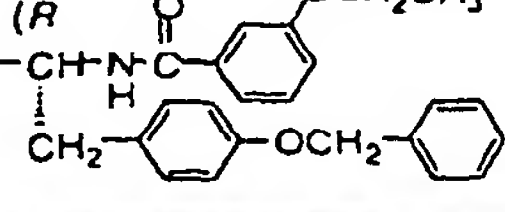
5	Compd. No.	$\begin{matrix} R^1 \\ \diagup \\ R^2 \end{matrix} (CH_2)_l$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{matrix} R^4 \\ \\ R^5 \end{matrix} (CH_2)_q G-R^6$
10	2091		2	2	1	-	H	
15	2092		2	2	1	-	H	
20	2093		2	2	1	-	H	
25	2094		2	2	1	-	H	
30	2095		2	2	1	-	H	
35	2096		2	2	1	-	H	
40	2097		2	2	1	-	H	
45	2098		2	2	1	-	H	
50	2099		2	2	1	-	H	
55	2100		2	2	1	-	H	
	2101		2	2	1	-	H	

Table 1.192

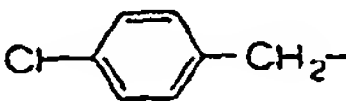
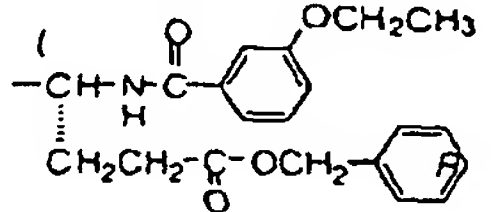
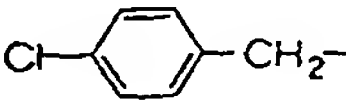
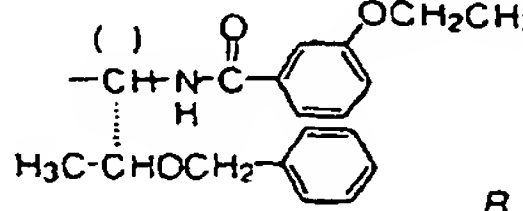
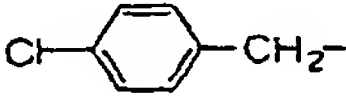
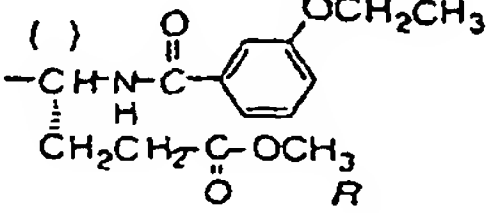
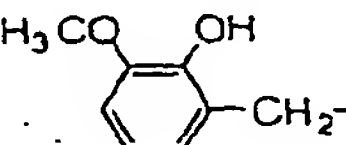
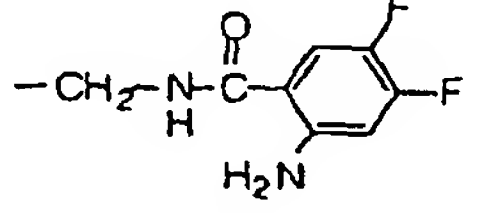
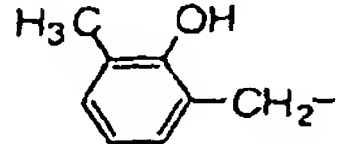
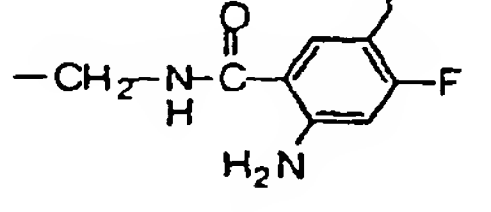
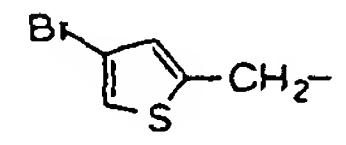
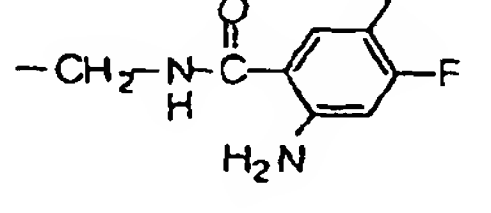
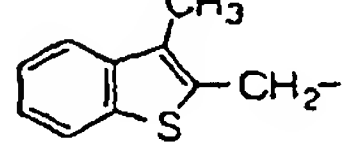
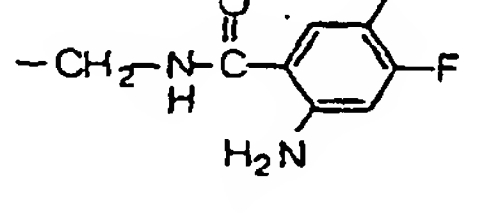
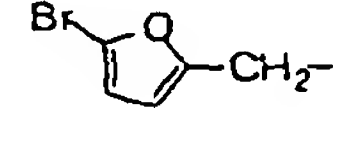
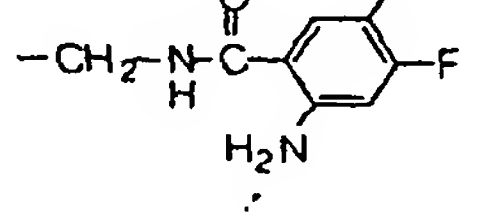
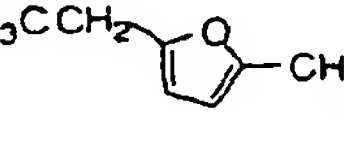
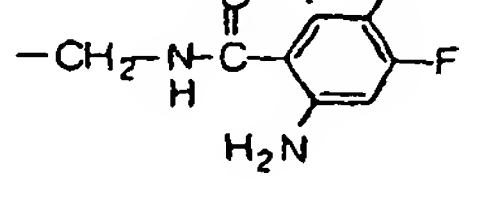
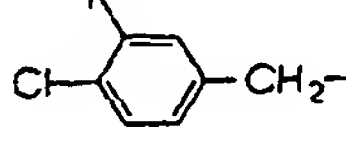
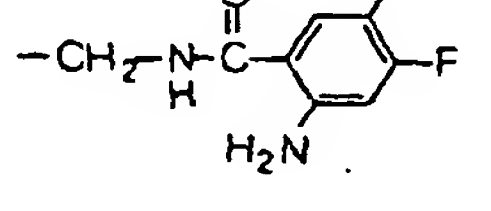
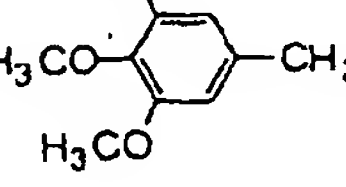
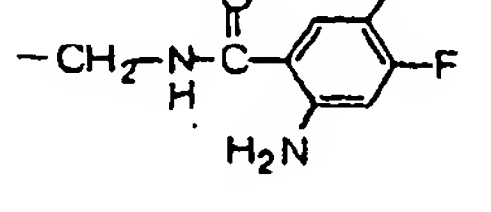
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
2102		2	2	1	-	H	
2103		2	2	1	-	H	
2104		2	2	1	-	H	
2105		2	2	1	-	H	
2106		2	2	1	-	H	
2107		2	2	1	-	H	
2108		2	2	1	-	H	
2109		2	2	1	-	H	
2110		2	2	1	-	H	
2111		2	2	1	-	H	
2112		2	2	1	-	H	

Table 1.193

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_k \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q G-R^6$
2113		2	2	1	-	H	
2114		2	2	1	-	H	
2115		2	2	1	-	H	
2116		2	2	1	-	H	
2117		2	2	1	-	H	
2118		1	2	0	R	H	
2119		1	2	0	R	H	
2120		1	2	0	R	H	
2121		1	2	0	R	H	
2122		1	2	0	R	H	
2123		1	2	0	R	H	

Table 1.194

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
2124		1	2	0	R	H	
2125		1	2	0	R	H	
2126		1	2	0	R	H	
2127		1	2	0	R	H	
2128		1	2	0	R	H	
2129		1	2	0	R	H	
2130		2	2	1	-	H	
2131		2	2	1	-	H	
2132		1	2	0	R	H	
2133		1	2	0	R	H	
2134		1	2	0	R	H	

Table 1.195

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j -$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
2135		1	2	0	R	H	
2136		1	2	0	R	H	
2137		1	2	0	R	H	
2138		1	2	0	R	H	
2139		1	2	0	R	H	
2140		2	2	1	-	H	
2141		2	2	1	-	H	
2142		2	2	1	-	H	
2143		2	2	1	-	H	
2144		2	2	1	-	H	
2145		2	2	1	-	H	

Table 1.196

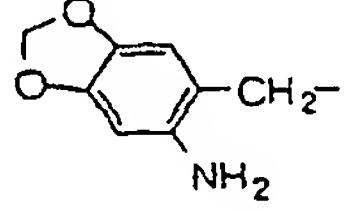
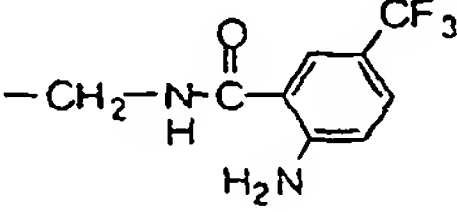
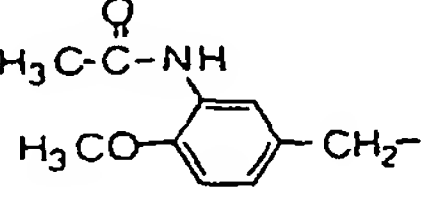
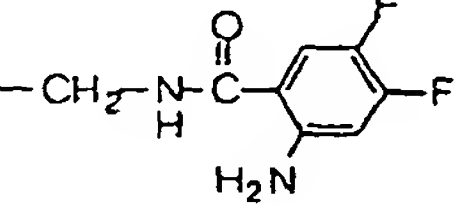
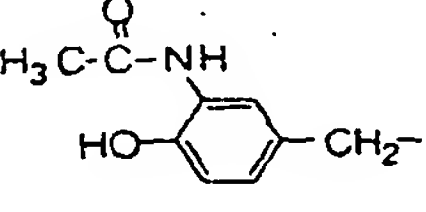
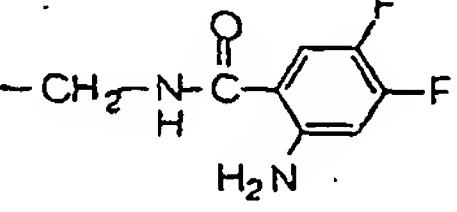
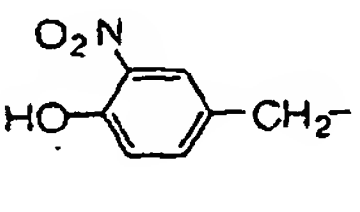
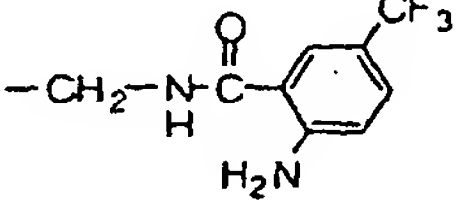
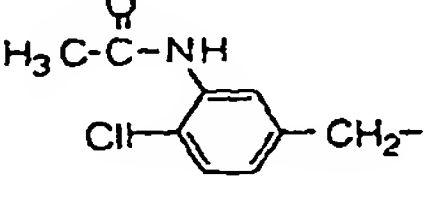
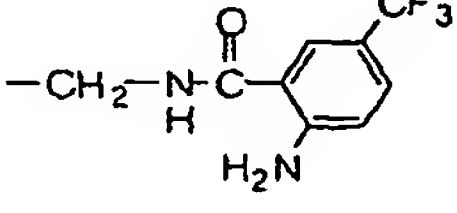
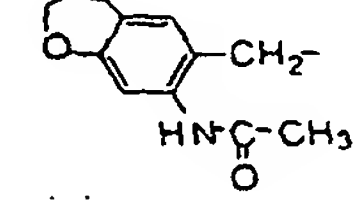
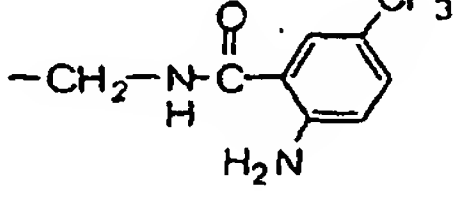
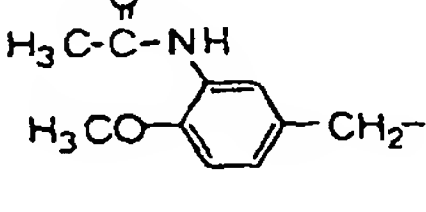
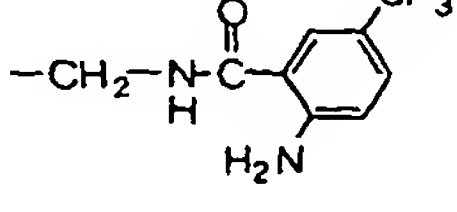
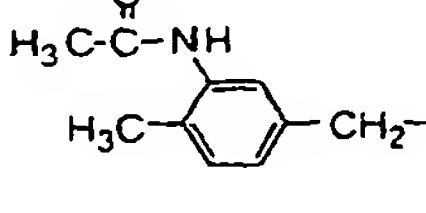
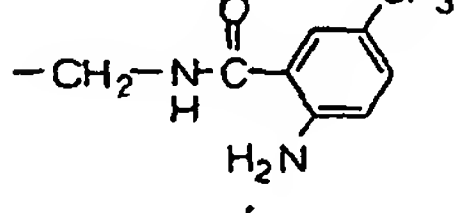
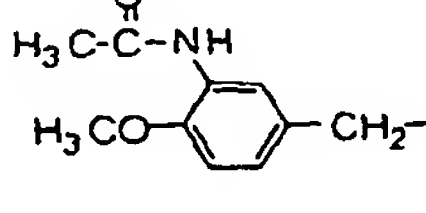
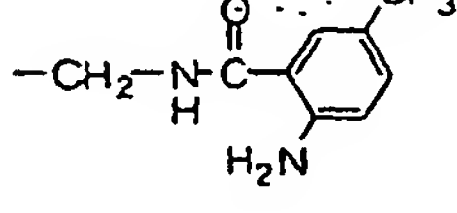
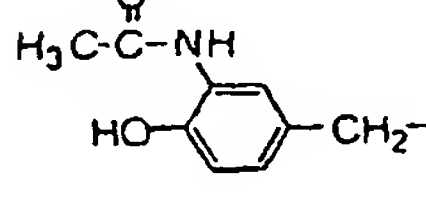
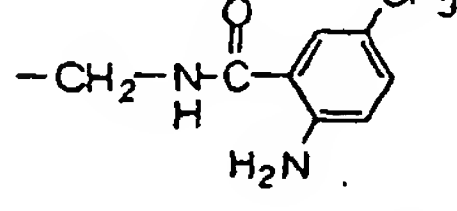
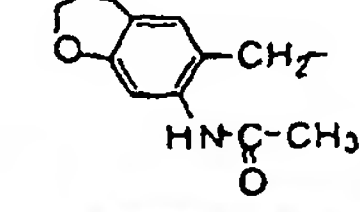
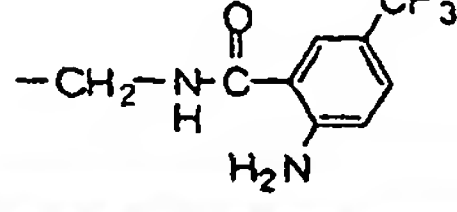
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
2146		2	2	1	-	H	
2147		2	2	1	-	H	
2148		2	2	1	-	H	
2149		1	2	0	R	H	
2150		1	2	0	R	H	
2151		1	2	0	R	H	
2152		1	2	0	R	H	
2153		1	2	0	R	H	
2154		2	2	1	-	H	
2155		2	2	1	-	H	
2156		2	2	1	-	H	

Table 1.197

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
2157		1	2	0	R	H	
2158		1	2	0	R	H	
2159		2	2	1	-	H	
2160		2	2	1	-	H	
2161		2	2	1	-	H	
2162		2	2	1	-	H	
2163		2	2	1	-	H	
2164		1	2	0	R	H	
2165		1	2	0	R	H	
2166		1	2	0	R	H	
2167		1	2	0	R	H	

Table 1.198

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
2168		1	2	0	R	H	
2169		1	2	0	R	H	
2170		1	2	0	R	H	
2171		1	2	0	R	H	
2172		1	2	0	R	H	
2173		1	2	0	R	H	
2174		1	2	0	R	H	
2175		1	2	0	R	H	
2176		1	2	0	R	H	
2177		1	2	0	R	H	
2178		1	2	0	R	H	

Table 1.199

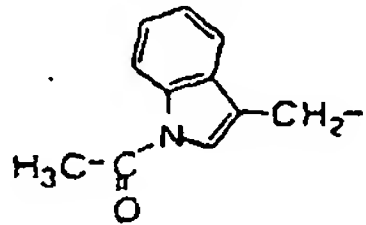
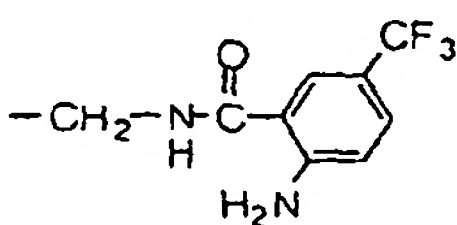
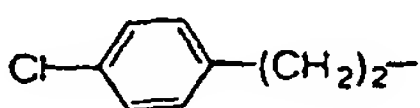
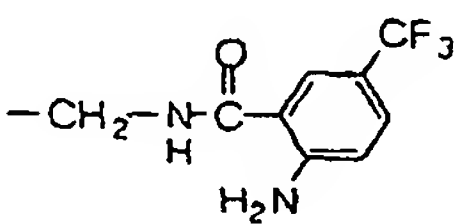
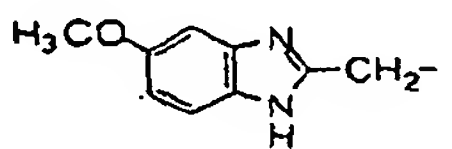
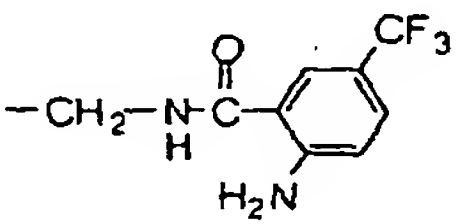
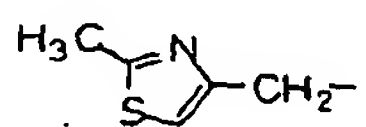
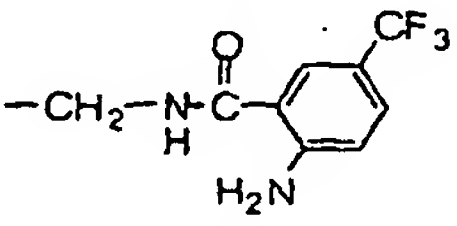
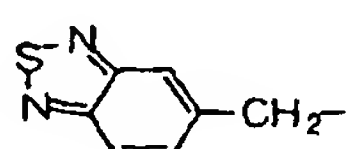
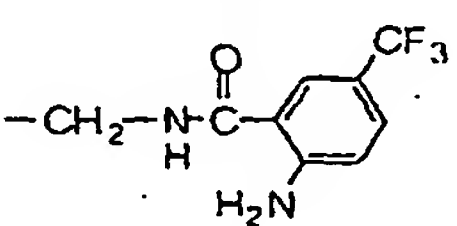
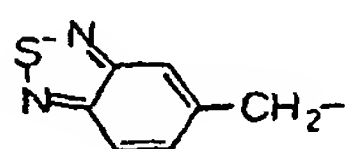
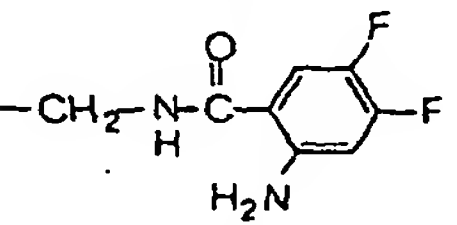
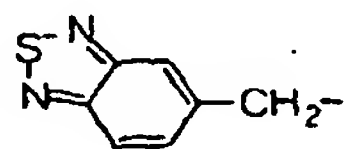
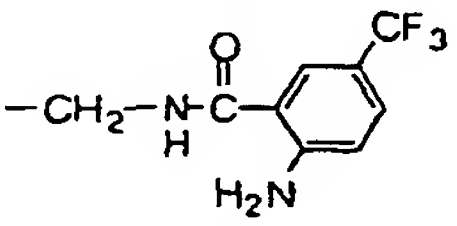
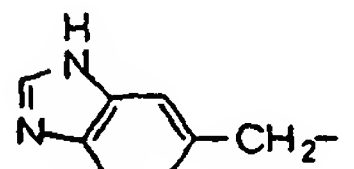
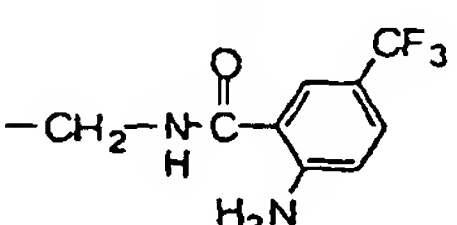
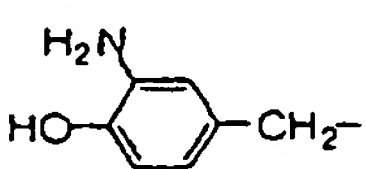
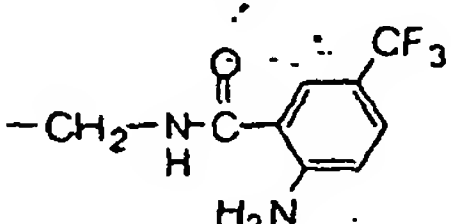
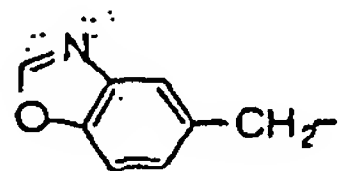
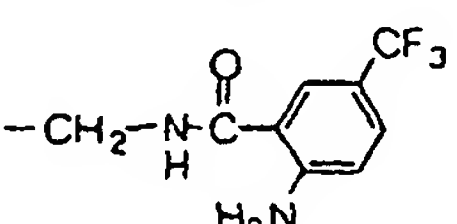
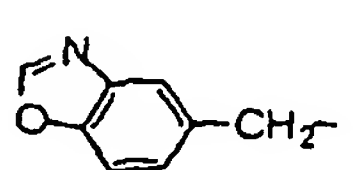
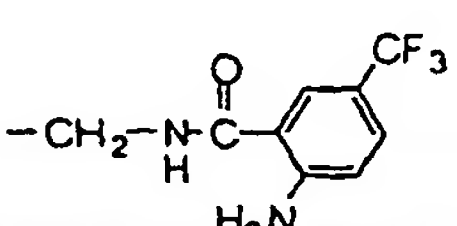
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_i \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
2179		1	2	0	R	H	
2180		1	2	0	R	H	
2181		1	2	0	R	H	
2182		1	2	0	R	H	
2183		1	2	0	R	H	
2184		2	2	1	-	H	
2185		2	2	1	-	H	
2186		2	2	1	-	H	
2187		1	2	0	R	H	
2188		2	2	1	-	H	
2189		1	2	0	R	H	

Table 1.200

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_l$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
2190		2	2	1	-	H	
2191		2	2	1	-	H	
2192		2	2	1	-	H	
2193		2	2	1	-	H	
2194		2	2	1	-	H	
2195		2	2	1	-	H	
2196		1	2	0	R	H	
2197		1	2	0	R	H	
2198		1	2	0	R	H	
2199		2	2	1	-	H	
2200		2	2	1	-	H	

Table 1.201

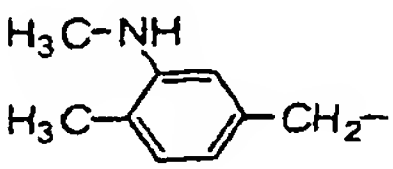
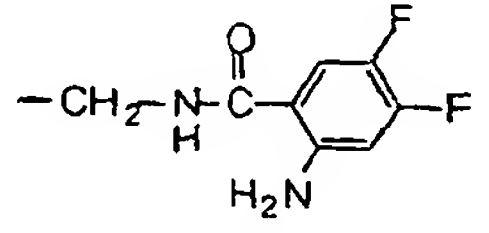
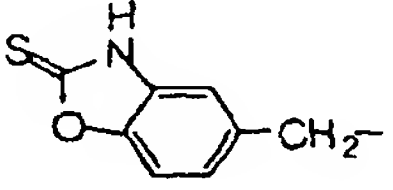
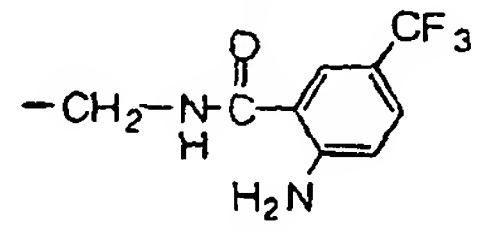
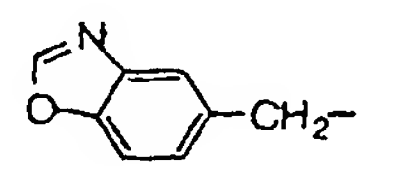
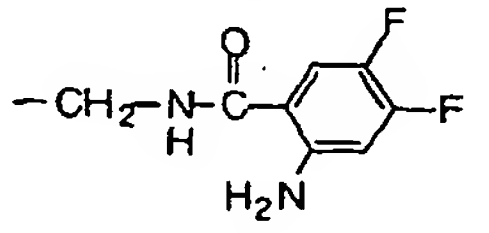
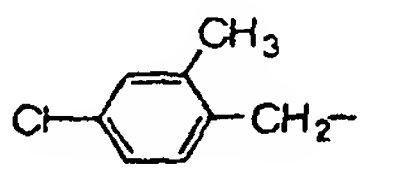
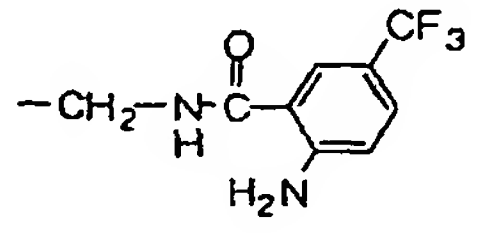
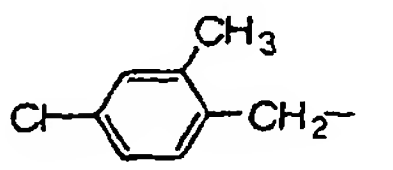
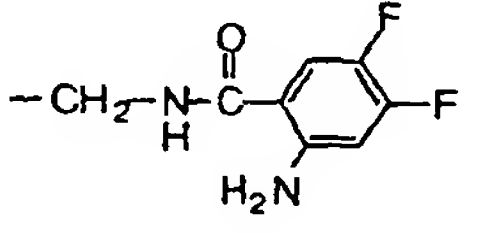
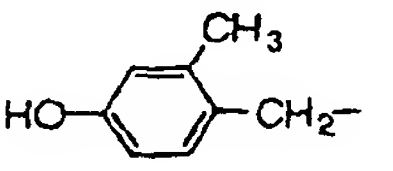
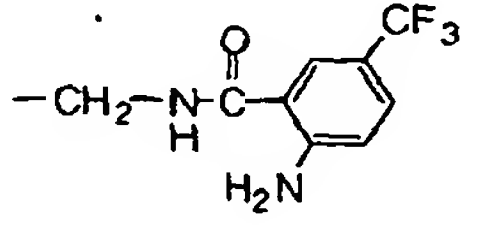
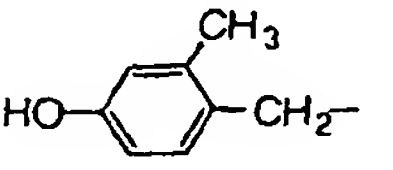
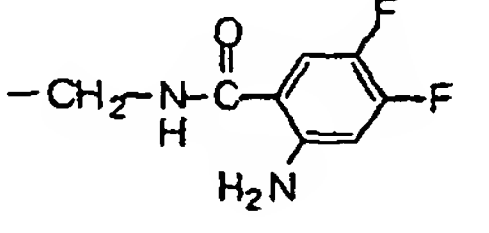
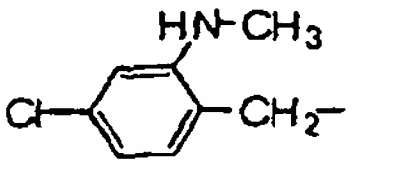
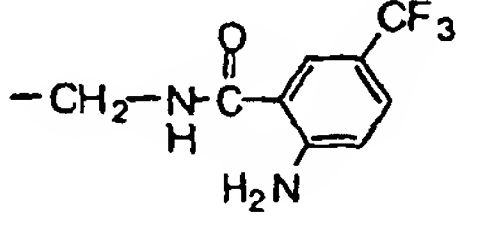
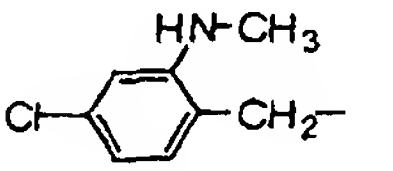
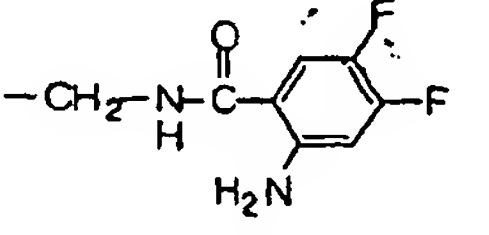
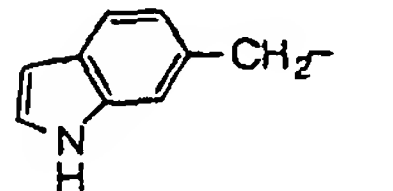
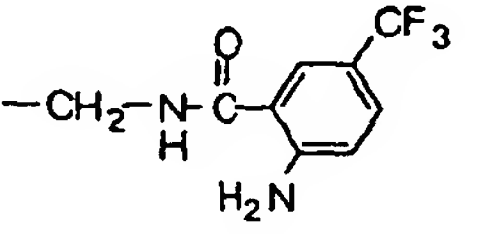
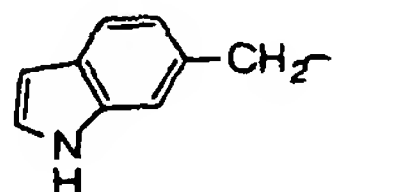
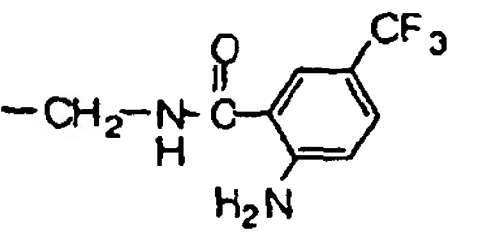
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
2201		2	2	1	-	H	
2202		1	2	0	R	H	
2203		2	2	1	-	H	
2204		2	2	1	-	H	
2205		2	2	1	-	H	
2206		2	2	1	-	H	
2207		2	2	1	-	H	
2208		2	2	1	-	H	
2209		2	2	1	-	H	
2210		1	2	0	R	H	
2211		2	2	1	-	H	

Table 1.202

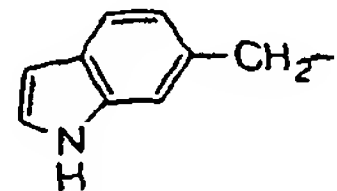
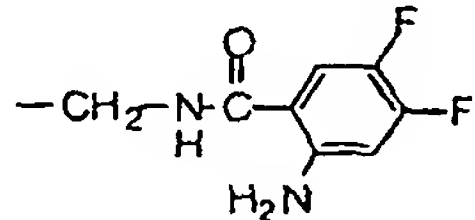
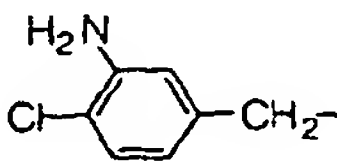
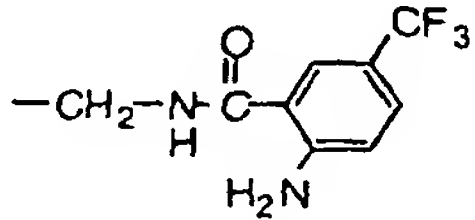
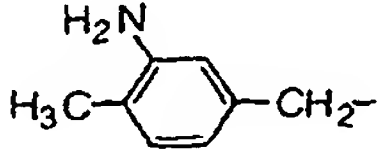
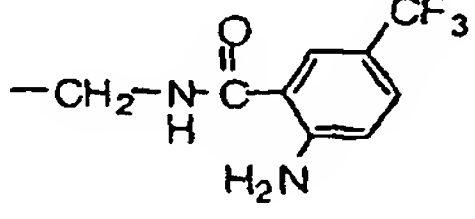
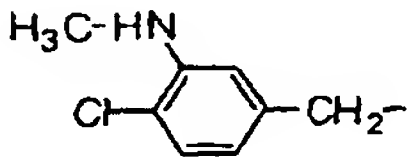
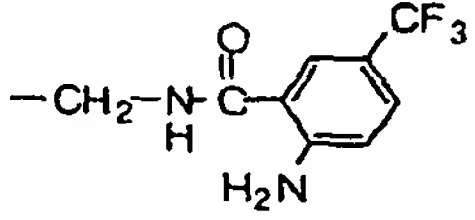
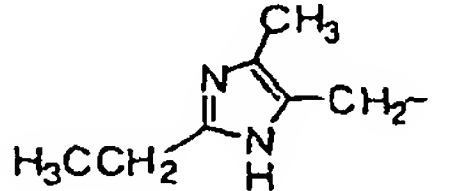
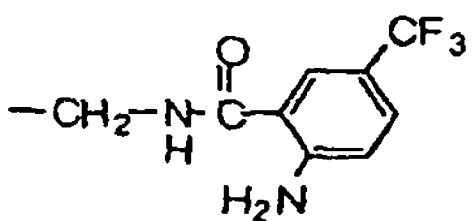
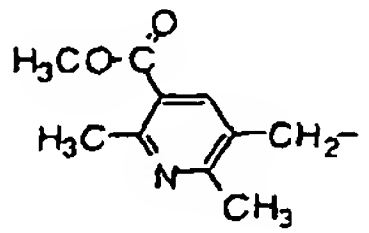
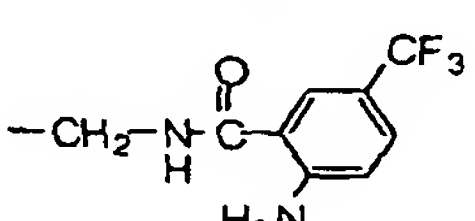
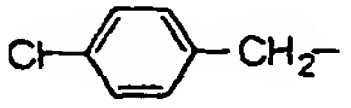
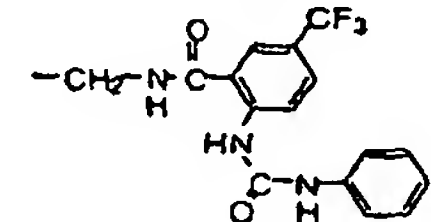
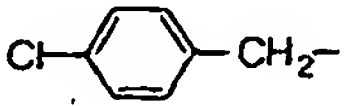
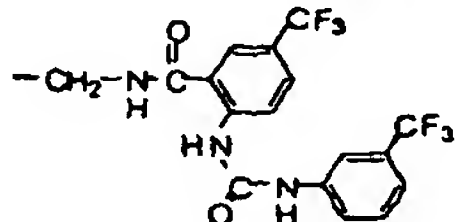
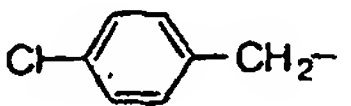
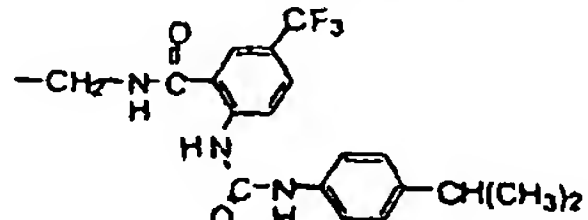
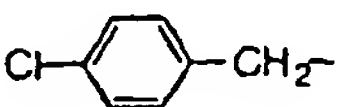
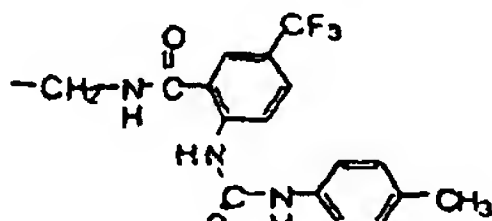
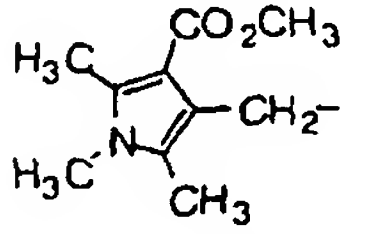
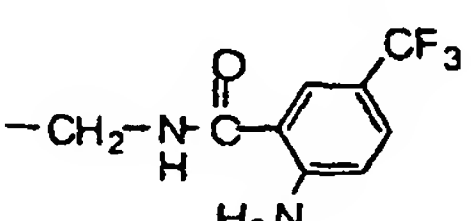
Compd. No.	$\begin{matrix} R^1 \\ R^2 \end{matrix} \text{---} (\text{CH}_2)_k \text{---}$	k	m	n	chirality	R^3	$\text{---} (\text{CH}_2)_p \text{---} \begin{matrix} R^4 \\ R^5 \end{matrix} \text{---} (\text{CH}_2)_q \text{---} \text{G---} R^6$
2212		2	2	1	-	H	
2213		2	2	1	-	H	
2214		2	2	1	-	H	
2215		1	2	0	R	H	
2216		1	2	0	R	H	
2217		1	2	0	R	H	
2218		1	2	0	R	H	
2219		1	2	0	R	H	
2220		1	2	0	R	H	
2221		1	2	0	R	H	
2222		1	2	0	R	H	

Table 1.203

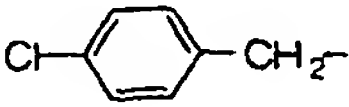
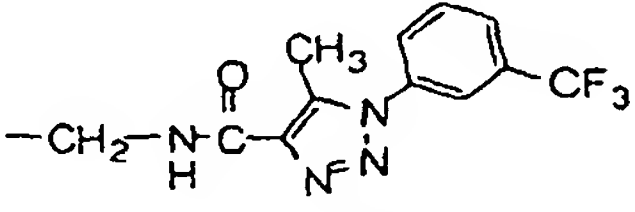
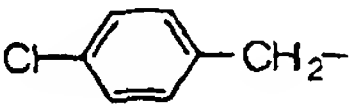
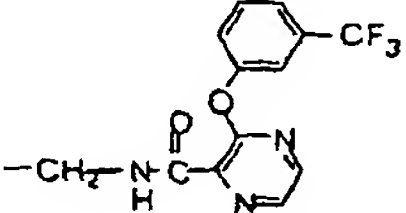
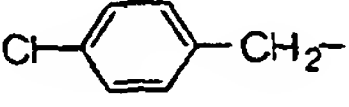
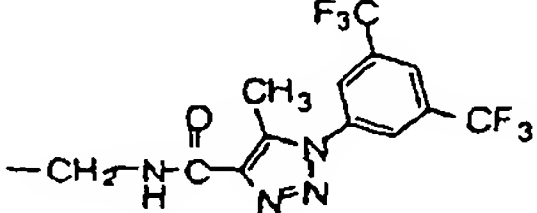
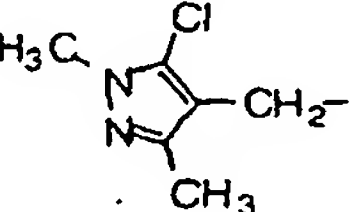
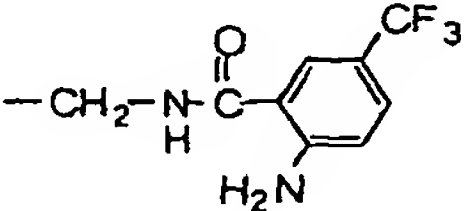
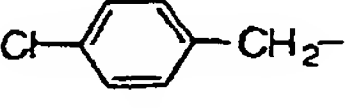
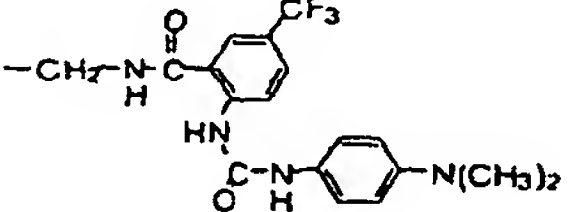
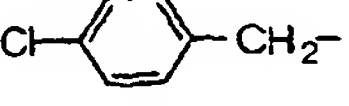
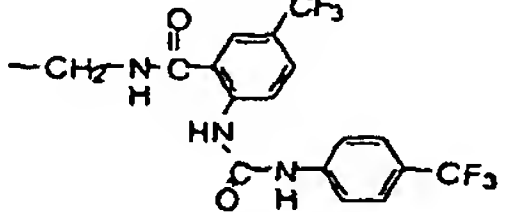
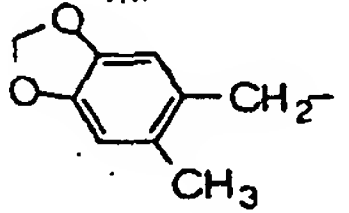
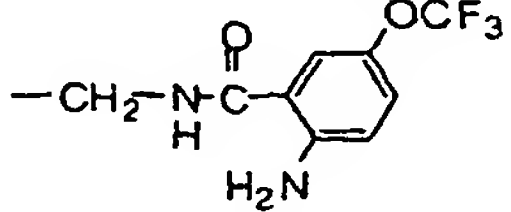
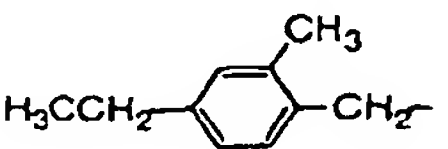
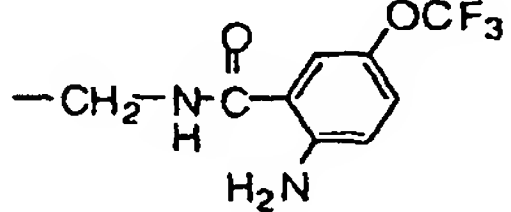
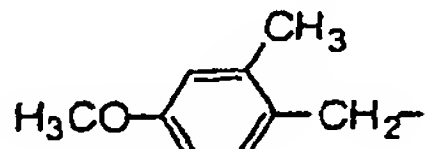
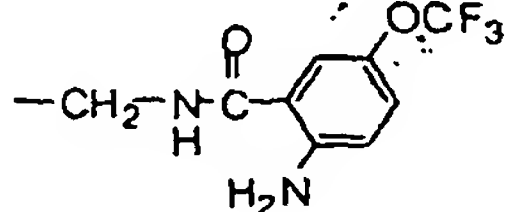
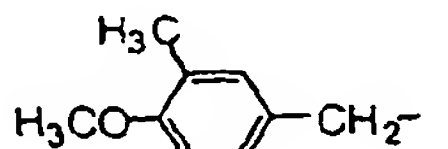
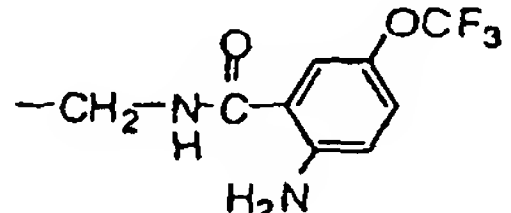
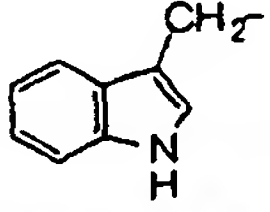
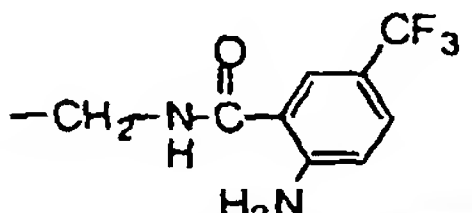
5 10 15 20 25 30 35 40 45 50 55	Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j- \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
	2223		1	2	0	R	H	
	2224		1	2	0	R	H	
	2225		1	2	0	R	H	
	2226		1	2	0	R	H	
	2227		1	2	0	R	H	
	2228		1	2	0	R	H	
	2229		1	2	0	R	H	
	2230		1	2	0	R	H	
	2231		1	2	0	R	H	
	2232		1	2	0	R	H	
	2233		1	2	0	R	H	

Table 1.204

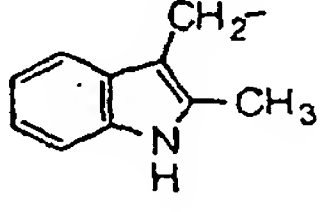
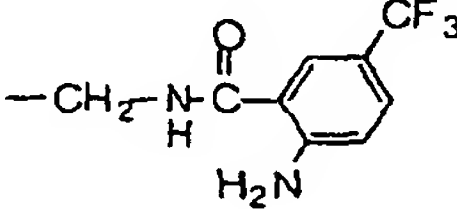
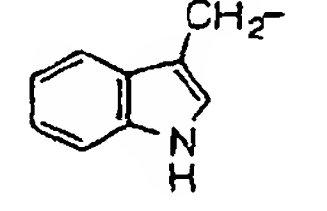
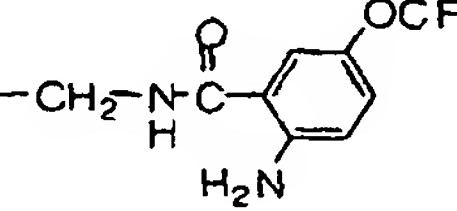
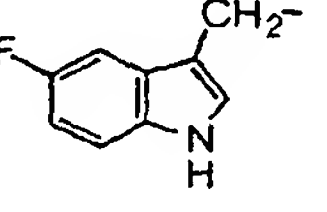
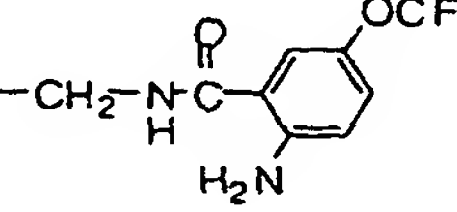
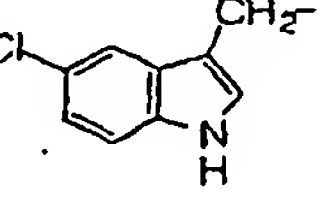
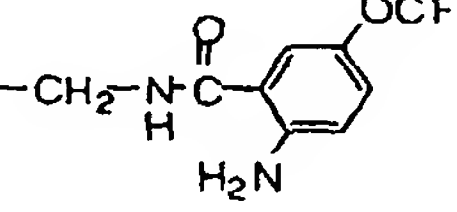
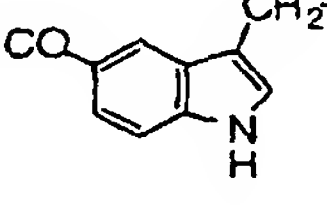
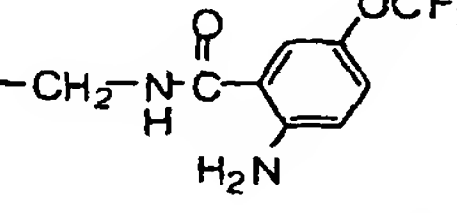
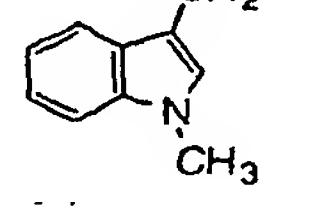
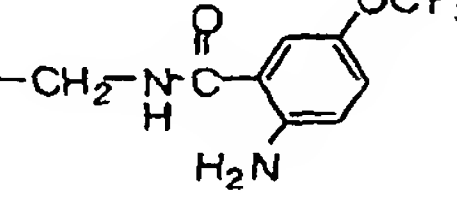
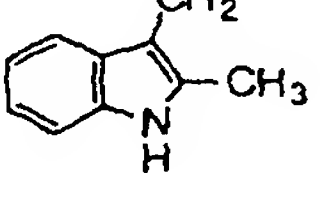
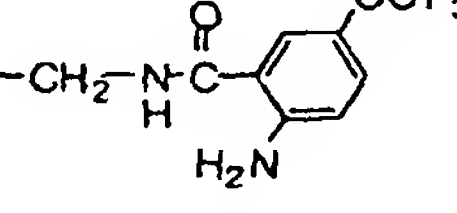
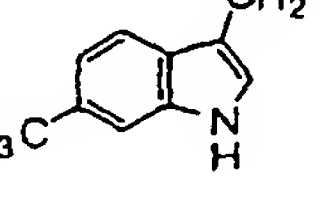
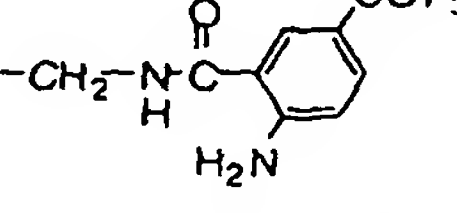
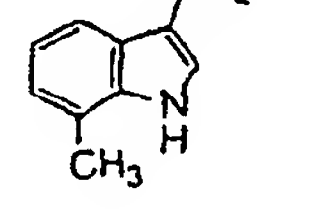
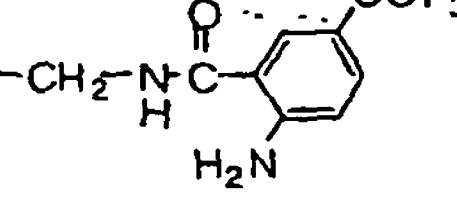
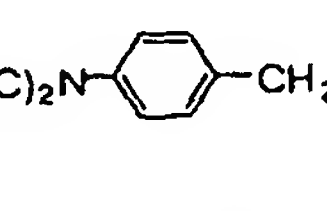
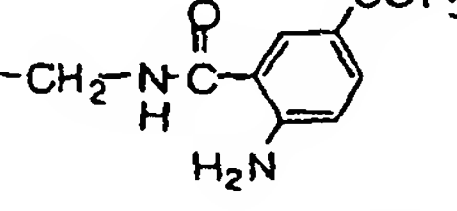
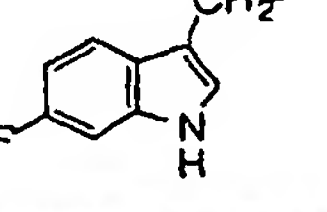
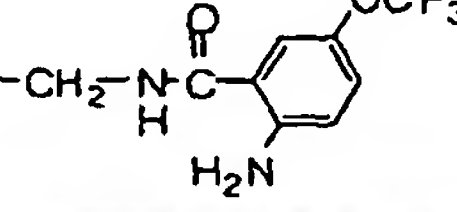
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ R^2 \end{array} (CH_2)_j$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
2234		1	2	0	R	H	
2235		1	2	0	R	H	
2236		1	2	0	R	H	
2237		1	2	0	R	H	
2238		1	2	0	R	H	
2239		1	2	0	R	H	
2240		1	2	0	R	H	
2241		1	2	0	R	H	
2242		1	2	0	R	H	
2243		1	2	0	R	H	
2244		1	2	0	R	H	

Table 1.205

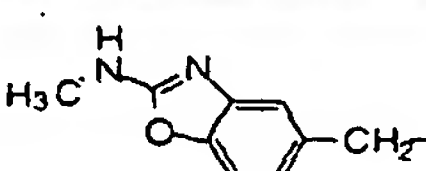
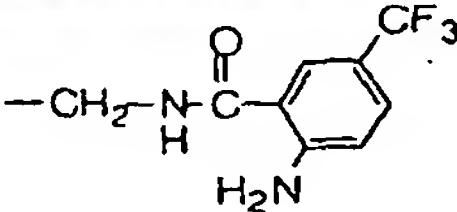
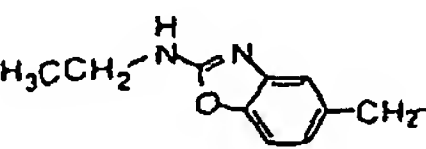
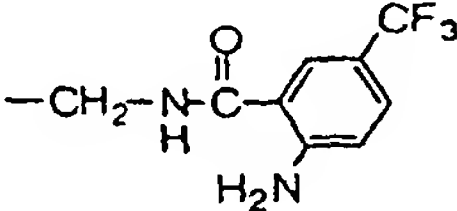
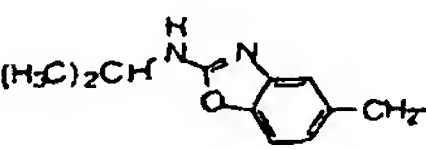
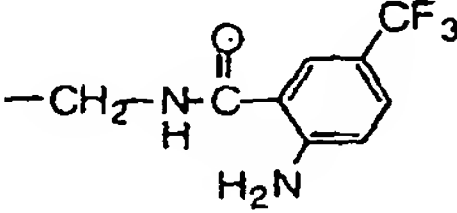
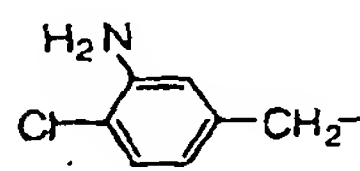
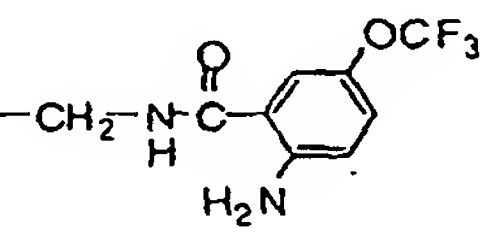
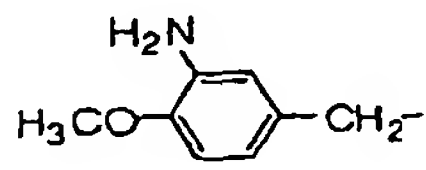
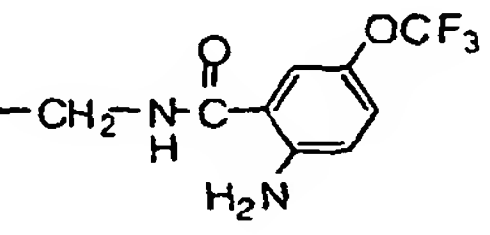
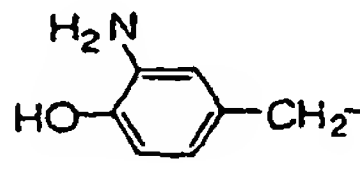
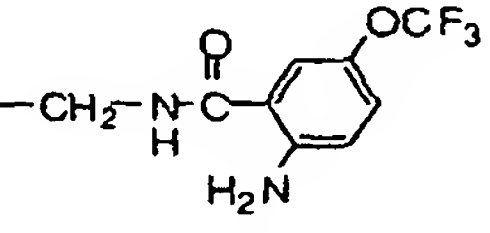
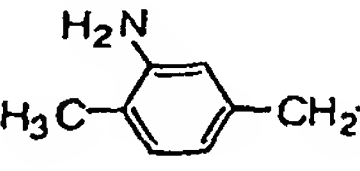
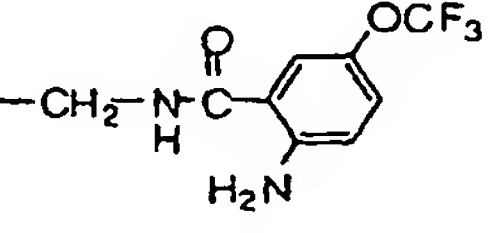
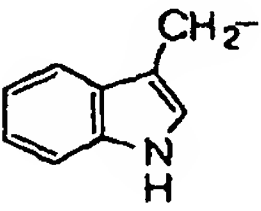
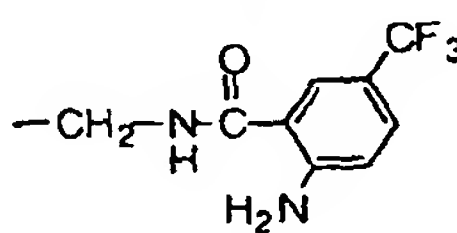
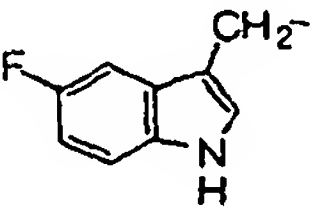
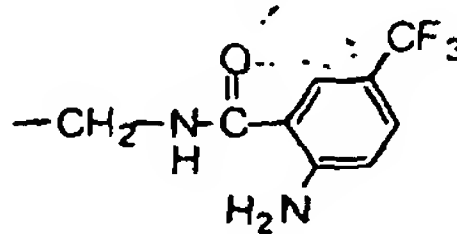
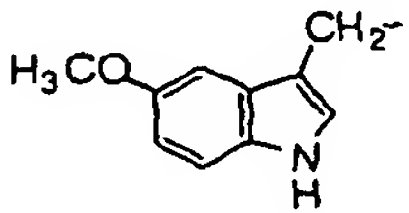
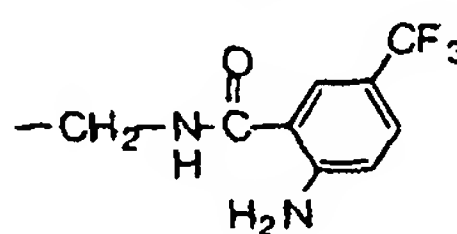
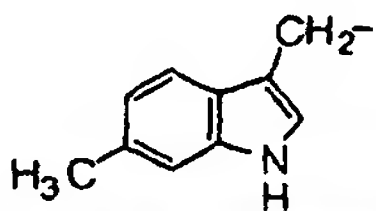
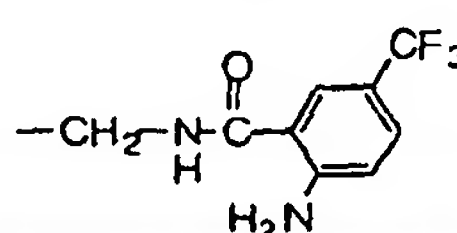
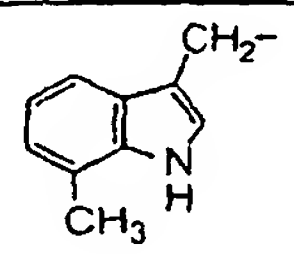
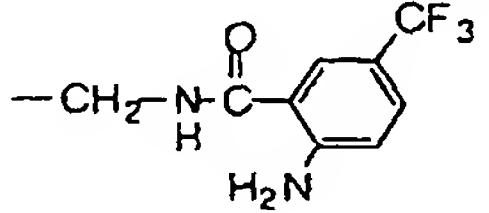
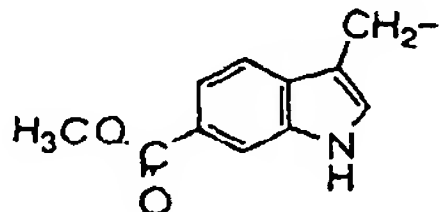
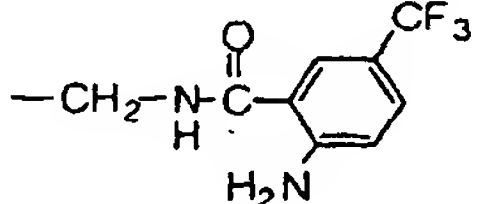
Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p \begin{array}{c} R^4 \\ \\ R^5 \end{array} (CH_2)_q - G - R^6$
2245		1	2	0	R	H	
2246		1	2	0	R	H	
2247		1	2	0	R	H	
2248		1	2	0	R	H	
2249		1	2	0	R	H	
2250		1	2	0	R	H	
2251		1	2	0	R	H	
2252		2	2	1	-	H	
2253		2	2	1	-	H	
2254		2	2	1	-	H	
2255		2	2	1	-	H	

Table 1.206

Compd. No.	$\begin{array}{c} R^1 \\ \diagup \\ (CH_2)_j \\ \diagdown \\ R^2 \end{array}$	k	m	n	chirality	R^3	$-(CH_2)_p-\begin{array}{c} R^4 \\ \\ (CH_2)_q-G-R^6 \\ \\ R^5 \end{array}$
2256		2	2	1	-	H	
2257		2	2	1	-	H	

[0101] The acid addition salts of the cyclic amine compounds are also used in the present invention. Examples of the acid include a mineral acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid or carbonic acid and an organic acid such as maleic acid, citric acid, malic acid, tartaric acid, fumaric acid, methanesulfonic acid, trifluoroacetic acid or formic acid.

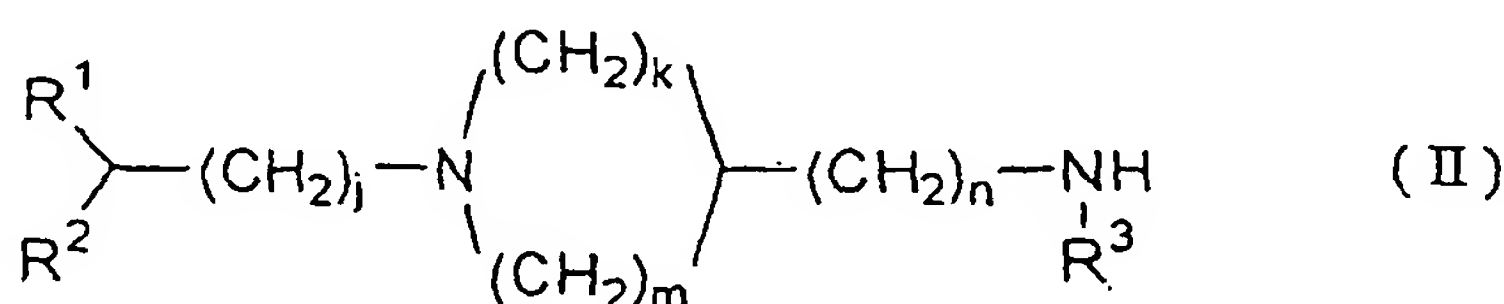
[0102] Furthermore, C_1 - C_6 alkyl addition salts of the cyclic amine compounds, for example, 1-(4-chlorobenzyl)-1-methyl-4-[[N-(3-trifluoromethylbenzoyl)glycyl]aminomethyl]piperidinium iodide are also used in the present invention. The alkyl group preferably includes methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, isopropyl, isobutyl, sec-butyl, tert-butyl, isopentyl, neopentyl, tert-pentyl, 2-methylpentyl and 1-ethylbutyl herein; however, methyl group, ethyl group or the like is especially preferable. A halide anion such as fluoride, chloride, bromide or iodide is preferable for a counter anion of an ammonium cation.

[0103] In the present invention, a racemate and all the possible optically active forms of the compounds represented by the above formula (I) can also be used.

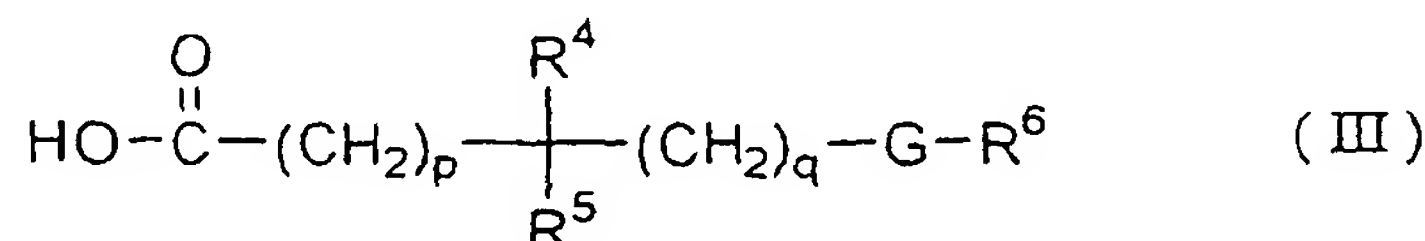
[0104] The compounds represented by the above formula (I) can be synthesized by using any of the following general preparation processes described in WO9925686:

(Preparation process 1)

[0105] A preparation process comprises reacting one equivalent of a compound represented by the following formula (II):



wherein R^1 , R^2 , R^3 , j , k , m and n are each the same as defined in the above formula (I), with 0.1 to 10 equivalents of a carboxylic acid represented by the following formula (III):



wherein R^4 , R^5 , R^6 , G , p and q are each the same as defined in the above formula (I), or a reactive derivative thereof in the absence or presence of a solvent.

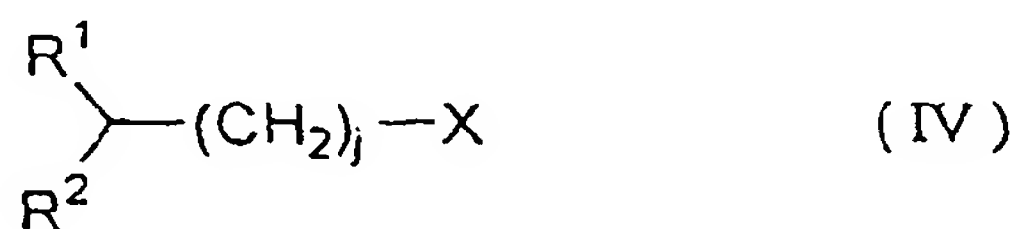
[0106] The "reactive derivative" of the carboxylic acid represented by the above formula (III) mean a carboxylic acid

derivative, for example, an acid halide, an acid anhydride or a mixed acid anhydride usually used in the synthetic organic chemistry field and having high reactivity.

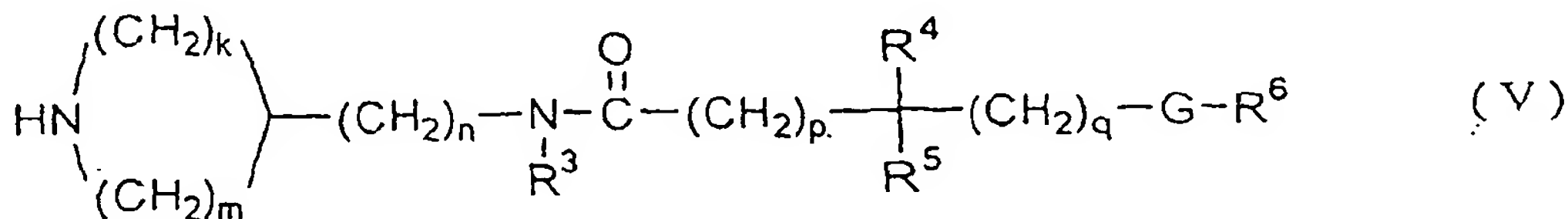
[0107] The reaction can more smoothly be made to proceed by suitably using an adequate amount of a dehydrating agent such as molecular sieve; a coupling reagent such as dicyclohexylcarbodiimide (DCC), N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide (EDCI or WSC), carbonyldiimidazole (CDI), N-hydroxysuccinimide (HOSu), N-hydroxybenzotriazole (HOBt), benzotriazol-1-yloxytris(pyrrolidinol) phosphonium hexafluorophosphate (PyBOP), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 2-(5-norbornene-2,3-dicarboxyimide)-1,1,3,3-tetramethyluronium tetrafluoroborate (TNTU), O-(N-succinimidyl)-1,1,3,3-tetramethyluronium hexafluorophosphate (TSTU) or bromotris(pyrrolidino)phosphonium hexafluorophosphate (PyBroP); a base such as an inorganic base such as potassium carbonate, calcium carbonate or sodium hydrogencarbonate; amines such as triethylamine, diisopropylethylamine or pyridine or a polymer supported base such as (piperidinomethyl)polystyrene, (morpholinomethyl)polystyrene, (dimethylaminomethyl)polystyrene or poly(4-vinylpyridine).

(Preparation process 2)

[0108] A preparation process comprises reacting one equivalent of an alkylating reagent represented by the following formula (IV):



wherein R^1 , R^2 and j are each the same as defined in the above formula (I); X is a halogen atom, an alkylsulfonyloxy group or an arylsulfonyloxy group, with 0.1 to 10 equivalents of a compound represented by the following formula (V):



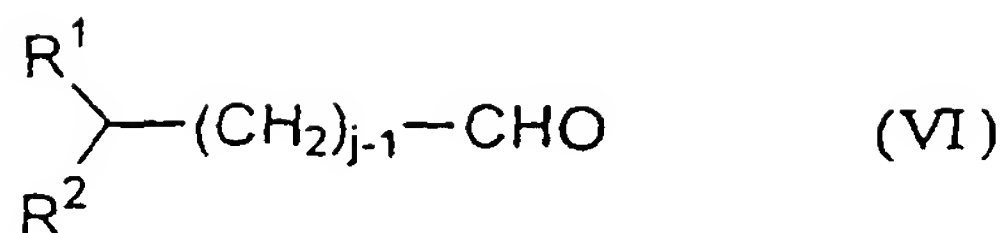
wherein R^3 , R^4 , R^5 , R^6 , G , k , m , n , p and q are each the same as defined in the above formula (I), in the absence or presence of a solvent.

[0109] The reaction can more smoothly be made to proceed by suitably using a base similar to that in the preparation process 1. Furthermore, the reaction sometimes can be promoted by the presence of an iodide such as potassium iodide or sodium iodide.

[0110] In the above formula (IV), X is a halogen atom, an alkylsulfonyloxy group or an arylsulfonyloxy group. Examples of the halogen atom preferably include a chlorine atom, a bromine atom and an iodine atom. Specific examples of the alkylsulfonyloxy group preferably include a methylsulfonyloxy group, a trifluoromethylsulfonyloxy group and the like, and the specific example of the arylsulfonyloxy group preferably includes tosyloxy group.

(Preparation process 3)

[0111] A preparation process comprises reacting one equivalent of an aldehyde represented by the following formula (VI):



wherein R^1 and R^2 are each the same as defined in the above formula (I); j is 1 or 2, or an aldehyde represented by the following formula (VII):

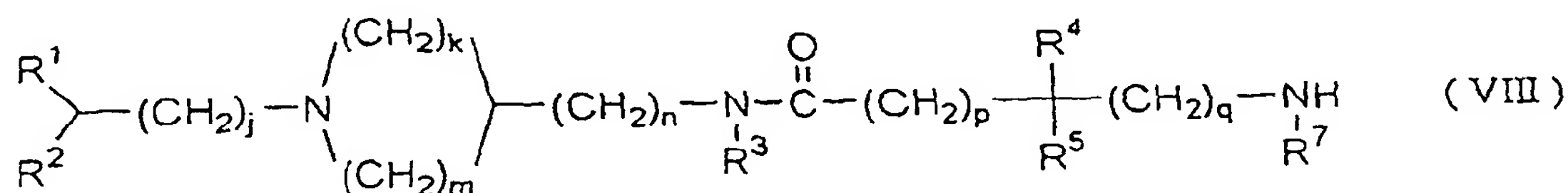


wherein R^1 is the same as defined for R^1 in the above formula (I); the compound corresponds to the case where j is 0, with 0.1 to 10 equivalents of a compound represented by the above formula (V) in the absence or presence of a solvent.

[0112] The reaction is usually called a reductive amination reaction and a catalytic hydrogenation reaction using a catalyst containing a metal such as palladium, platinum, nickel or rhodium, a hydrogenation reaction using a complex hydride such as lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride and borane, an electrolytic reducing reaction or the like can be used as reductive conditions.

(Preparation process 4)

[0113] A preparation process comprises reacting one equivalent of a compound represented by the following formula (VIII):



wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^7 , j , k , m , n , p and q are each the same as defined in the above formula (I), with 0.1 to 10 equivalents of a carboxylic acid or a sulfonic acid represented by the following formula (IX):



wherein R^6 is the same as defined in the above formula (I); A is a carbonyl group or a sulfonyl group, or a reactive derivative thereof in the absence or presence of a solvent

[0114] The reactive derivative of the carboxylic acid or sulfonic acid represented by the above formula (IX) means a carboxylic acid derivative or sulfonic acid derivative, for example, an acid halide, an acid anhydride or a mixed acid anhydride usually used in the synthetic organic chemistry field and having high reactivity. The reaction can more smoothly be made to proceed by suitably using a dehydrating agent, a coupling reagent or a base similar to that in the above preparation process 1.

(Preparation process 5)

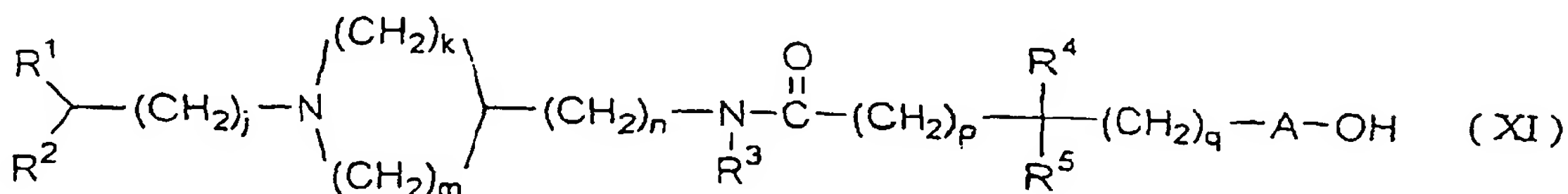
[0115] A preparation process comprises reacting one equivalent of a compound represented by the above formula (VIII) with 0.1 to 10 equivalents of an isocyanate or an isothiocyanate represented by the following formula (X):



wherein R^6 is the same as defined in the above formula (I); Z is an oxygen atom or a sulfur atom, in the absence or presence of a solvent.

(Preparation process 6)

[0116] A preparation process comprises reacting one equivalent of a compound represented by the following formula (XI):



wherein R^1 , R^2 , R^3 , R^4 , R^5 , j , k , m , n , p and q are each the same as defined in the above formula (I); A is a carbonyl group or a sulfonyl group, with 0.1 to 10 equivalents of an amine represented by the following formula (XII):



wherein R^6 is the same as defined for R^6 in the above formula (I), in the absence or presence of a solvent.

[0117] The reaction can more smoothly be made to proceed by suitably using a dehydrating agent, a coupling reagent or a base similar to that in the above preparation process 1.

[0118] In the above preparation processes 1 to 6, when a substrate used for each reaction has substituents regarded as usually reacting under respective reaction conditions in the organic synthetic chemistry or having adverse effects on the reaction, the functional groups can be protected with a known suitable protecting group, and the substrate can be used for the reaction and then deprotected by a conventional known method to afford the objective compound.

[0119] In addition, the compounds used in the present invention can be obtained by further converting (single or plural) substituents of the compound produced by the above preparation process 1 - 6 using a known reaction usually used in the organic synthetic chemistry, for example, an alkylation reaction, an acylation reaction or a reduction reaction.

[0120] In the above respective preparation processes, a halogenated hydrocarbon such as dichloromethane or chloroform, an aromatic hydrocarbon such as benzene or toluene, ethers such as diethyl ether or tetrahydrofuran, esters such as ethyl acetate, an aprotic polar solvent such as dimethylformamide, dimethyl sulfoxide or acetonitrile and alcohols such as methanol, ethanol or isopropyl alcohol are suitably used as a reaction solvent according to the reaction.

[0121] In each of the preparation processes, the reaction temperature is within the range of -78 to $+150$ $^{\circ}\text{C}$, preferably within the range of 0 to 100 $^{\circ}\text{C}$. After completing the reaction, the objective cyclic amine compounds represented by the above formula (I) can be isolated by carrying out usual isolating and purifying operations, i.e., concentration, filtration, extraction, solid-phase extraction, recrystallization or chromatography. The compounds can be converted into their pharmaceutically acceptable acid addition salts thereof or their C_1 - C_6 alkyl addition salts thereof according to a usual method.

Examples

[0122] The present invention is detailed specifically based on Examples; however, the present invention is not restricted to compounds described in the Examples. The Compound number (Compd. No.) assigned to each compound in the following Examples corresponds to the Compd. No. assigned to each compound cited as a preferred specific example in Tables 1.1 to 1.206.

[Reference Example 1] Synthesis of 3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride

[0123] 4-Chlorobenzyl chloride (4.15 g, 25.8 mmol) and $i\text{Pr}_2\text{NEt}$ (6.67 g, 51.6 mmol) were added to a DMF (50 mL) solution of 3-[(tert-butoxycarbonyl)amino]pyrrolidine (4.81 g, 25.8 mmol). The reaction mixture was stirred at 70 $^{\circ}\text{C}$ for 15 hours, and the solvent was removed under reduced pressure. The objective 3-[(tert-butoxycarbonyl)amino]-1-(4-chlorobenzyl)pyrrolidine (6.43 g, 80%) was obtained as an off-white solid by recrystallization (acetonitrile, 50 mL). ^1H NMR (CDCl_3 , 300MHz) δ 1.37 (s, 9 H), 1.5-1.7 (br, 1 H), 2.1-2.4 (m, 2 H), 2.5-2.7 (m, 2 H), 2.83 (br, 1 H), 3.57 (s, 2 H), 4.1-4.3 (br, 1 H), 4.9-5.1 (br, 1 H), 7.15-7.35 (br, 4 H); the purity was determined by RPLC/MS (98%). ESI/MS

m/e 311.0 (M⁺+H, C₁₆H₂₄ClN₂O₂).

[0124] To a methanol solution (80 mL) of the 3-[(tert-butoxycarbonyl)amino]-1-(4-chlorobenzyl)pyrrolidine (6.38 g, 20.5 mmol), was added 1 M HCl-Et₂O (100 mL). The resulting mixture was stirred at 25 °C for 15 hours. The solvent was removed under reduced pressure to provide a solid, which was purified by recrystallization (methanol/acetonitrile = 1:2, 130 mL) to thereby afford 3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride (4.939 g, 85%) as a white powder. ¹H NMR (d₆-DMSO, 300MHz) δ 3.15 (br, 1 H), 3.3-3.75 (br·m, 4 H), 3.9 (br, 1 H), 4.05 (br, 1 H), 4.44 (br, 1 H), 4.54 (br, 1 H), 7.5-7.7 (m, 4 H), 8.45 (br, 1 H), 8.60 (br, 1 H); the purity was determined by RPLC/MS (>99%). ESI/MS m/e 211.0 (M⁺+H, C₁₁H₁₆ClN₂).

[0125] Optically active (R)-3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride and (S)-3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride were synthesized by using the respective corresponding starting materials according to the above method. The products exhibited the same ¹H NMR as that of the above racemate.

[Example 1] Synthesis of 3-(N-benzoylglycyl)amino-1-(4-chlorobenzyl)pyrrolidine (Compd. No. 1)

[0126] N-Benzoylglycine (9.3 mg, 0.055 mmol), 3-ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride (ED-Cl) (1.05 mg) and 1-hydroxybenzotriazole hydrate (HOBt) (7.4 mg) were added to a chloroform (2.5 mL) solution of 3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride (14.2 mg, 0.050 mmol) and triethylamine (15.2 mg). The resulting reaction mixture was stirred at 25 °C for 16 hours and then washed with a 2 M aqueous solution of NaOH (2mL×2) and brine. After filtration through a PTFE membrane filter, the solvent was removed under reduced pressure to provide 3-(N-benzoylglycyl)amino-1-(4-chlorobenzyl)pyrrolidine (Compd. No. 1) as an off-white oil (17.7 mg, 95%). The purity was determined by RPLC/MS (95%). ESI/MS m/e 372.0 (M⁺+H, C₂₀H₂₂ClN₃O₂).

[Examples 2 to 32]

[0127] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method in Example 1. The data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 2.

Table 2

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
2	2	C ₂₁ H ₂₄ ClN ₃ O ₂	386	16.4	85
3	3	C ₁₉ H ₂₁ ClN ₄ O ₂	373	18.7	100
4	4	C ₂₁ H ₂₁ ClF ₃ N ₃ O ₂	440	57.2	69
5	82	C ₂₂ H ₂₃ ClF ₃ N ₃ O ₂	454	5.6	11
6	85	C ₂₁ H ₂₄ ClN ₃ O ₂	386	22.6	59
7	86	C ₂₁ H ₂₃ ClN ₄ O ₄	431	21.2	98
8	214	C ₂₂ H ₂₅ ClN ₂ O ₂	385	23.9	62
9	215	C ₂₃ H ₂₇ ClN ₂ O ₃	415	17.4	84
10	216	C ₂₀ H ₂₃ ClN ₂ O ₂ S	391	21.6	Q
11	217	C ₂₃ H ₂₇ ClN ₂ O ₄	431	15.3	66
12	218	C ₂₃ H ₂₇ ClN ₂ O ₂	399	12.8	64
13	219	C ₂₂ H ₂₄ ClFN ₂ O ₃	419	18.1	86
14	220	C ₂₂ H ₂₅ ClN ₂ O ₂	385	16.4	85
15	221	C ₂₁ H ₂₃ ClN ₂ O ₂	371	14.9	80
16	222	C ₂₁ H ₂₂ Cl ₂ N ₂ O ₂	405	13.3	65
17	223	C ₂₅ H ₃₁ ClN ₂ O ₃	443	18.4*	63
18	224	C ₂₀ H ₂₃ ClN ₂ O ₃ S	407	11.2	28

Notes: * indicates "yield (mg) of trifluoroacetate".
Q means "Quantitative".

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Table 2 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
19	225	C ₂₂ H ₂₆ ClN ₃ O ₂	400	22.7	Q
20	226	C ₂₃ H ₂₈ ClN ₃ O ₃	430	21.0	98
21	227	C ₂₂ H ₂₅ Cl ₂ N ₃ O ₂	434	21.9	100
22	228	C ₂₃ H ₂₈ ClN ₃ O ₃	430	20.8	97
23	229	C ₂₅ H ₃₂ ClN ₃ O ₂	462	25.4	Q
24	230	C ₂₆ H ₃₁ ClFN ₃ O ₂	472	26.0	Q
25	231	C ₂₄ H ₂₈ ClN ₃ O ₃	442	30.3*	Q
26	232	C ₂₂ H ₃₂ ClN ₃ O ₂	406	3.9	19
27	233	C ₂₃ H ₂₈ ClN ₃ O ₂	414	8.5	41
28	234	C ₂₂ H ₂₇ ClN ₄ O ₂	415	7.3	35
29	235	C ₂₄ H ₂₉ Cl ₂ N ₃ O ₂	462	9.0	39
30	236	C ₂₅ H ₂₉ ClN ₄ O ₃ S	501	17.4	69
31	237	C ₂₁ H ₂₄ ClN ₃ O ₃	402	14.2	71
32	238	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₃	436	23.4	Q

Notes: * indicates "yield (mg) of trifluoroacetate".

Q means "Quantitative".

[Reference Example 2] Synthesis of (R)-3-[(N-tert-butoxycarbonyl)glycyl]amino-1-(4-chlorobenzyl)pyrrolidine

[0128] A mixture of (R)-3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride (4.54 g, 16.0 mmol) with a 2 M solution (80 mL) of NaOH and ethyl acetate (80 mL) was stirred, and the organic layer was separated to extract the aqueous layer with ethyl acetate (80 mL×2). The organic layers were combined, dried over anhydrous sodium sulfate, then filtered and concentrated to thereby afford free (R)-3-amino-1-(4-chlorobenzyl)pyrrolidine (3.35 g, 99%).

[0129] To a dichloromethane (80 mL) solution of the (R)-3-amino-1-(4-chlorobenzyl)pyrrolidine (3.35 g, 16 mmol), were added triethylamine (2.5 mL, 17.6 mmol), N-tert-butoxycarbonylglycine (2.79 g, 16.0 mmol), EDCI (3.07 g, 16.0 mmol) and HOBt (12.16 g, 16 mmol). The resulting reaction mixture was stirred at 25 °C for 16 hours, and a 2 M solution (80 mL) of NaOH was then added thereto. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (100 mL×3). The organic layers were combined, washed with water (100 mL×2) and brine (100 mL), dried over anhydrous sodium sulfate, filtered, concentrated and purified by column chromatography (SiO₂, ethyl acetate) to thereby provide the objective (R)-3- [N-(tert-butoxycarbonyl)glycyl]amino-1-(4-chlorobenzyl)pyrrolidine (5.40 g, 92%).

[Reference Example 3] Synthesis of (R)-1-(4-chlorobenzyl)-3-(glycylamino)pyrrolidine

[0130] A 4 M HCl dioxane (38 mL) solution was added to a methanol (60 mL) solution of (R)-3-[N-(tert-butoxycarbonyl)glycyl]amino-1-(4-chlorobenzyl)pyrrolidine (5.39 g, 14.7 mmol). The resulting solution was stirred at room temperature for 2 hours. The reaction mixture was concentrated, and a 2 M solution (80 mL) of NaOH was added. The mixture solution was extracted with dichloromethane (80 mL×3), and the extracts were combined, dried over anhydrous sodium sulfate, concentrated and purified by column chromatography (SiO₂, ethyl acetate/ethanol/triethylamine = 90:5:5) to afford (R)-3-(glycylamino)-1-(4-chlorobenzyl)pyrrolidine (3.374 g, 86%) ¹H NMR (CDCl₃, 274MHz) δ 1.77 (dd, J = 1.3 and 6.9 Hz, 1 H), 2.20-3.39 (m, 2 H), 2.53 (dd, J = 3.3 and 9.6 Hz, 1 H), 2.62 (dd, J = 6.6 and 9.6 Hz, 1 H), 2.78-2.87 (m, 1 H), 3.31 (s, 2 H), 3.57(s, 2 H), 4.38-4.53 (br, 1 H), 7.18-7.32 (m, 4 H), 7.39(br, s, 1 H).

[0131] Other 3-acylamino-1-(4-chlorobenzyl)pyrrolidines were synthesized by using the respective corresponding starting materials and reactants according to the methods of Reference Examples 2 and 3.

(S)-1-(4-chlorobenzyl)-3-(glycylamino)pyrrolidine: 3.45 g, 79% (two steps).

(R)-3-(β-alanyl-amino)-1-(4-chlorobenzyl)pyrrolidine: 3.79 g, 85% (two steps).

(S)-3-(β-alanyl-amino)-1-(4-chlorobenzyl)pyrrolidine: 3.72 g, 86% (two steps)

(R)-3-[(S)-alanyl-amino]-1-(4-chlorobenzyl)pyrrolidine: 368 mg, 65% (two steps).

(R)-3-[(R)-alanyl-amino]-1-(4-chlorobenzyl)pyrrolidine: 425 mg, 75% (two steps).

(R)-3-[(2S)-2-amino-3-thienylpropanoyl]amino-1-(4-chlorobenzyl)pyrrolidine: 566 mg, 78% (two step).

(R)-3-[(2R)-2-amino-3-thienylpropanoyl]amino-1-(4-chlorobenzyl)pyrrolidine: 5.85 mg, 81% (two steps).

(R)-3-(2-amino-2-methylpropanoyl)amino-1-(4-chlorobenzyl)pyrrolidine: 404 mg, 66% (two steps).

(R)-3-[(2S)-2-amino-4-(methylsulfonyl)butanoyl]amino-1-(4-chlorobenzyl)pyrrolidine: 535 mg, 72% (two steps).

[0132] Furthermore, (R)-3-(glycylamino)-1-(4-methylbenzyl)pyrrolidine, (R)-1-(4-bromobenzyl)-3-(glycylamino)pyrrolidine, (R)-1-(2,4-dimethylbenzyl)-3-(glycylamino)pyrrolidine and (R)-1-(3,5-dimethylisoxazol-4-ylmethyl)-3-(glycylamino)pyrrolidine were synthesized by using the respective corresponding starting materials and reactants according to the methods of Reference Examples 1, 2 and 3.

[0133] (R)-3-(glycylamino)-1-(4-methylbenzyl)pyrrolidine : 4.65 g, yield 62% (yield from 3-[(tert-butoxycarbonyl)amino]pyrrolidine).

[0134] (R)-1-(4-bromobenzyl)-3-(glycylamino)pyrrolidine: 2.55 g, yield 68% (yield from (R)-3-amino-1-(4-bromobenzyl)pyrrolidine); ^1H NMR (CDCl_3 , 270MHz) δ 1.37-1.78 (m, 3 H), 2.23-2.39 (m, 2 H), 2.50-2.67 (m, 2 H), 2.80-2.89 (m, 1 H), 3.32 (s, 2 H), 3.58 (s, 2 H), 4.39-4.55 (m, 1 H), 7.21 (d, J = 6.5 Hz, 2 H), 7.45 (d, J = 6.5 Hz, 2 H).

[0135] (R)-1-(2,4-dimethylbenzyl)-3-(glycylamino)pyrrolidine: 1.56 g, yield 58% (yield from 3-[(tert-butoxycarbonyl)amino]pyrrolidine); ^1H NMR (CDCl_3 , 270MHz) δ 1.55-1.78 (m, 3 H), 2.30 (s, 3 H), 2.23-2.31 (m, 2 H), 2.33 (s, 3 H), 2.51-2.63 (m, 2 H), 2.78-2.87 (m, 1 H), 3.30 (s, 2 H), 3.55 (s, 2 H), 4.38-4.60 (m, 1 H), 6.95 (d, J = 7.6 Hz, 1 H), 6.97 (s, 1 H), 7.13 (d, J = 7.6 Hz, 1 H), 7.43 (br-s, 1 H).

[0136] (R)-1-(3,5-dimethylisoxazol-4-ylmethyl)-3-(glycylamino)pyrrolidine: 3.14 g, yield 45% (yield from 3-[(tert-butoxycarbonyl)amino]pyrrolidine).

[Example 33] Synthesis of (S)-3-[N-[3,5-bis(trifluoromethyl)benzoyl]glycyl]amino-1-(4-chlorobenzyl)pyrrolidine (Compd. No. 5).

[0137] A chloroform solution (0.4 mL) of 3,5-bis(trifluoromethyl)benzoyl chloride (0.060 mmol) was added to a chloroform (1.0 mL) solution of (S)-1-(4-chlorobenzyl)-3-(glycylamino)pyrrolidine (0.050 mmol) and triethylamine (0.070 mmol). The resulting reaction mixture was stirred at room temperature for 2.5 hours, and an (aminomethyl)polystyrene resin (1.04 mmol/g, 50 mg, 50 mmol) was then added. The prepared mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered, and the resin was washed with dichloromethane (0.5 mL). The filtrate and the washing were combined, and dichloromethane (4 mL) was added. The resulting solution was washed with a 2 M aqueous solution (0.5 mL) of NaOH and concentrated to thereby provide (S)-3-[N-[3,5-bis(trifluoromethyl)benzoyl]glycyl]amino-1-(4-chlorobenzyl)pyrrolidine (Compd. No. 5) (14.4 mg, 57%). The purity was determined by RPLC/MS (97%). ESI/MS m/e 508.0 ($\text{M}^+\text{+H}$, $\text{C}_{22}\text{H}_{20}\text{ClF}_6\text{N}_3\text{O}_2$).

[Examples 34 to 239]

[0138] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 33. Data of ESI/MS, yields (mg) and yields (%) are collectively shown on Table 3.

Table 3

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
34	5	$\text{C}_{22}\text{H}_{20}\text{ClF}_6\text{N}_3\text{O}_2$	508.0	14.4	57
35	6	$\text{C}_{21}\text{H}_{21}\text{ClF}_3\text{N}_3\text{O}_2$	440.0	17.0	77
36	7	$\text{C}_{20}\text{H}_{21}\text{BrClN}_3\text{O}_2$	450.0	17.7	79
37	8	$\text{C}_{20}\text{H}_{21}\text{ClFN}_3\text{O}_2$	390.0	12.7	65
38	9	$\text{C}_{20}\text{H}_{20}\text{Cl}_3\text{N}_3\text{O}_2$	440.0	39.0	Q
39	10	$\text{C}_{21}\text{H}_{24}\text{ClN}_3\text{O}_3$	402.5	23.5	Q
40	11	$\text{C}_{22}\text{H}_{26}\text{ClN}_3\text{O}_4$	432.5	22.4	Q
41	12	$\text{C}_{22}\text{H}_{26}\text{ClN}_3\text{O}_4$	432.5	15.9	74
42	13	$\text{C}_{21}\text{H}_{21}\text{ClF}_3\text{N}_3\text{O}_2$	440.0	13.1	60
43	14	$\text{C}_{21}\text{H}_{24}\text{ClN}_3\text{O}_2$	386.0	16.4	85
44	15	$\text{C}_{20}\text{H}_{21}\text{Cl}_2\text{N}_3\text{O}_2$	406.0	15.7	77

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Table 3 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	45	C ₂₁ H ₂₄ ClN ₃ O ₂	402.0	28.2	Q
	46	C ₂₀ H ₂₀ Cl ₃ N ₃ O ₂	442.0	35.6	Q
	47	C ₂₁ H ₂₁ ClN ₄ O ₂	397.5	22.8	Q
10	48	C ₂₁ H ₂₂ ClN ₃ O ₄	416.0	16.3	78
	49	C ₂₁ H ₂₀ ClF ₄ N ₃ O ₂	458.0	24.9	Q
	50	C ₂₁ H ₂₀ ClF ₄ N ₃ O ₂	458.0	17.9	78
15	51	C ₂₁ H ₂₀ ClF ₄ N ₃ O ₂	458.0	9.4	41
	52	C ₂₁ H ₂₀ ClF ₄ N ₃ O ₂	458.0	15.4	67
	53	C ₂₁ H ₂₁ ClF ₃ N ₃ O ₃	456.0	20.7	91
20	54	C ₂₁ H ₂₀ ClF ₄ N ₃ O ₂	458.0	18.5	81
	55	C ₂₀ H ₂₁ ClN ₄ O ₄	417.0	21.9	Q
	56	C ₂₀ H ₂₁ ClN ₄ O ₄	417.0	16.8	81
25	57	C ₂₀ H ₂₁ ClN ₄ O ₄	417.0	6.8	33
	58	C ₂₂ H ₂₀ ClF ₆ N ₃ O ₂	508.0	20.8	82
	59	C ₂₁ H ₂₁ ClF ₃ N ₃ O ₂	440.0	15.2	69
30	60	C ₂₀ H ₂₁ BrClN ₃ O ₂	450.0	15.6	69
	61	C ₂₀ H ₂₁ ClFN ₃ O ₂	390.0	11.8	61
	62	C ₂₀ H ₂₀ Cl ₃ N ₃ O ₂	440.0	15.8	72
35	63	C ₂₁ H ₂₄ ClN ₃ O ₃	402.5	33.8	Q
	64	C ₂₂ H ₂₆ ClN ₃ O ₄	432.5	56.1	Q
	65	C ₂₂ H ₂₆ ClN ₃ O ₄	432.5	37.6	Q
40	66	C ₂₁ H ₂₁ ClF ₃ N ₃ O ₂	440.0	12.6	57
	67	C ₂₁ H ₂₄ ClN ₃ O ₂	386.0	12.3	64
	68	C ₂₀ H ₂₁ Cl ₂ N ₃ O ₂	406.0	15.9	78
45	69	C ₂₁ H ₂₄ ClN ₃ O ₂	402.0	11.6	58
	70	C ₂₀ H ₂₀ Cl ₃ N ₃ O ₂	442.0	17.8	81
	71	C ₂₁ H ₂₁ ClN ₄ O ₂	397.5	22.4	Q
50	72	C ₂₁ H ₂₂ ClN ₃ O ₄	416.0	30.1	Q
	73	C ₂₁ H ₂₀ ClF ₄ N ₃ O ₂	458.0	13.4	59
	74	C ₂₁ H ₂₀ ClF ₄ N ₃ O ₂	458.0	13.2	58
55	75	C ₂₁ H ₂₀ ClF ₄ N ₃ O ₂	458.0	14.4	63
	76	C ₂₁ H ₂₁ ClF ₃ N ₃ O ₃	456.0	16.4	72
	77	C ₂₁ H ₂₀ ClF ₄ N ₃ O ₂	458	16.5	72
55	78	C ₂₀ H ₂₁ ClN ₄ O ₄	417.0	12.5	60
	79	C ₂₁ H ₂₀ ClF ₄ N ₃ O ₂	458.0	26.3	Q
	80	C ₂₀ H ₂₁ BrClN ₃ O ₂	450.0	8.6	38
55	81	C ₂₀ H ₂₁ ClFN ₃ O ₂	390.5	4.1	21
	82	C ₂₀ H ₂₁ Cl ₂ N ₃ O ₂	406.0	5.4	27

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Table 3 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	83	C ₂₀ H ₂₀ Cl ₃ N ₃ O ₂	440.0	8.8	40
	84	C ₂₀ H ₂₀ BrCl ₄ N ₃ O ₂	440.0	7.7	35
	85	C ₂₁ H ₂₄ ClN ₃ O ₂	386.0	4.8	25
10	86	C ₂₂ H ₂₆ ClN ₃ O ₄	429.5	4.9	23
	87	C ₂₀ H ₂₁ Cl ₂ N ₃ O ₂	406.0	4.1	20
	88	C ₂₀ H ₂₁ BrClN ₃ O ₂	452.0	3.5	16
15	89	C ₂₆ H ₂₆ ClN ₃ O ₂	448.5	7.3	33
	90	C ₂₁ H ₂₁ ClF ₃ N ₃ O ₂	440.0	7.1	32
	91	C ₂₁ H ₂₄ ClN ₃ O ₂	386.0	10.4	54
20	92	C ₂₂ H ₂₆ ClN ₃ O ₂	400.5	6.0	30
	93	C ₂₁ H ₂₁ ClN ₄ O ₂	397.0	7.0	35
	94	C ₂₄ H ₂₄ ClN ₃ O ₂	422.0	7.7	36
25	95	C ₂₄ H ₂₄ ClN ₃ O ₂	422.0	6.3	30
	96	C ₂₀ H ₂₀ ClF ₂ N ₃ O ₂	408.0	4.7	23
	97	C ₂₀ H ₂₀ ClF ₂ N ₃ O ₂	408.0	7.8	38
30	98	C ₂₀ H ₂₀ ClF ₂ N ₃ O ₂	408.0	7.3	36
	99	C ₂₀ H ₂₀ ClF ₂ N ₃ O ₂	408.0	9.1	45
	100	C ₂₂ H ₂₆ ClN ₃ O ₄	429.0	5.6	26
35	101	C ₂₁ H ₂₁ ClF ₃ N ₃ O ₂	456.0	6.2	27
	102	C ₂₁ H ₂₁ ClF ₃ N ₃ O ₂	456.5	16.8	74
	103	C ₂₂ H ₂₄ ClN ₃ O ₄	430.0	16.4	76
40	104	C ₂₁ H ₂₀ ClF ₄ N ₃ O ₂	458.0	16.1	70
	105	C ₂₁ H ₂₀ ClF ₄ N ₃ O ₂	458.0	17.0	74
	106	C ₂₀ H ₁₉ ClF ₃ N ₃ O ₂	426.0	16.2	76
45	107	C ₂₀ H ₁₉ ClF ₃ N ₃ O ₂	426.0	18.0	85
	108	C ₂₂ H ₂₀ ClF ₆ N ₃ O ₂	508.0	18.8	74
	109	C ₂₂ H ₂₀ ClF ₆ N ₃ O ₂	508.0	16.4	65
50	110	C ₂₂ H ₂₆ ClN ₃ O ₂	400.0	13.9	70
	111	C ₂₀ H ₂₁ ClN ₄ O ₄	417.0	16.0	77
	112	C ₂₀ H ₂₁ ClN ₄ O ₄	417.0	21.6	Q
55	113	C ₂₃ H ₂₂ ClF ₆ N ₃ O ₂	522.0	17.5	67
	114	C ₂₂ H ₂₃ ClF ₃ N ₃ O ₂	454.0	13.9	61
	115	C ₂₁ H ₂₃ BrClN ₃ O ₂	466.0	15.4	66
55	116	C ₂₁ H ₂₃ ClFN ₃ O ₂	404.0	10.7	53
	117	C ₂₁ H ₂₂ Cl ₃ N ₃ O ₂	456.0	13.7	60
	118	C ₂₂ H ₂₆ ClN ₃ O ₃	416.0	38.4	Q
55	119	C ₂₃ H ₂₈ ClN ₃ O ₄	446.0	25.2	Q
	120	C ₂₃ H ₂₈ ClN ₃ O ₄	446.0	16.5	74

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Table 3 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	121	C ₂₂ H ₂₃ ClF ₃ N ₃ O ₂	454.0	16.3	72
	122	C ₂₂ H ₂₆ ClN ₃ O ₂	400.5	16.7	84
	123	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	11.2	53
10	124	C ₂₂ H ₂₆ ClN ₃ O ₂	416.5	11.8	57
	125	C ₂₁ H ₂₂ Cl ₃ N ₃ O ₂	454.0	14.8	65
	126	C ₂₂ H ₂₃ ClN ₄ O ₂	411.0	9.5	46
15	127	C ₂₂ H ₂₄ ClN ₃ O ₄	430.5	13.2	61
	128	C ₂₂ H ₂₂ ClF ₄ N ₃ O ₂	472.0	13.1	56
	129	C ₂₂ H ₂₂ ClF ₄ N ₃ O ₂	472.0	36.5	Q
20	130	C ₂₂ H ₂₂ ClF ₄ N ₃ O ₂	472.0	22.8	97
	131	C ₂₂ H ₂₂ ClF ₄ N ₃ O ₂	472.0	20.1	85
	132	C ₂₂ H ₂₃ ClF ₃ N ₃ O ₃	470.0	27.4	Q
25	133	C ₂₂ H ₂₂ ClF ₄ N ₃ O ₂	472.0	18.5	78
	134	C ₂₁ H ₂₃ ClN ₄ O ₄	431.0	11.9	55
	135	C ₂₁ H ₂₃ ClN ₄ O ₄	431.0	23.9	Q
30	136	C ₂₁ H ₂₃ ClN ₄ O ₄	431.0	24.4	Q
	137	C ₂₃ H ₂₂ ClF ₆ N ₃ O ₂	522.0	9.5	36
	138	C ₂₂ H ₂₃ ClF ₃ N ₃ O ₂	454.0	3.9	17
35	139	C ₂₁ H ₂₃ BrClN ₃ O ₂	466.0	7.5	32
	140	C ₂₁ H ₂₃ ClFN ₃ O ₂	404.0	6.1	30
	141	C ₂₁ H ₂₂ Cl ₃ N ₃ O ₂	456.0	6.6	29
40	142	C ₂₂ H ₂₆ ClN ₃ O ₃	416.0	4.8	23
	143	C ₂₃ H ₂₈ ClN ₃ O ₄	446.0	6.4	29
	144	C ₂₃ H ₂₈ ClN ₃ O ₄	446.0	24.6	Q
45	145	C ₂₂ H ₂₃ ClF ₃ N ₃ O ₂	454.0	5.2	23
	146	C ₂₂ H ₂₆ ClN ₃ O ₂	400.5	4.4	22
	147	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	7.8	37
50	148	C ₂₂ H ₂₆ ClN ₃ O ₂	416.5	14.1	68
	149	C ₂₁ H ₂₂ Cl ₃ N ₃ O ₂	454.0	5.4	24
	150	C ₂₂ H ₂₃ ClN ₄ O ₂	411.0	34.0	Q
55	151	C ₂₂ H ₂₄ ClN ₃ O ₄	430.5	32.0	Q
	152	C ₂₂ H ₂₂ ClF ₄ N ₃ O ₂	472.0	4.6	19
	153	C ₂₂ H ₂₂ ClF ₄ N ₃ O ₂	472.0	10.4	44
	154	C ₂₂ H ₂₂ ClF ₄ N ₃ O ₂	472.0	7.3	31
	155	C ₂₂ H ₂₂ ClF ₄ N ₃ O ₂	472.0	13.5	57
	156	C ₂₂ H ₂₃ ClF ₃ N ₃ O ₃	470.0	15.1	64
	157	C ₂₂ H ₂₂ ClF ₄ N ₃ O ₂	472.0	8.6	36
	158	C ₂₁ H ₂₃ ClN ₄ O ₄	431.0	4.4	20

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Table 3 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	159	C ₂₁ H ₂₃ ClN ₄ O ₄	431.0	32.0	Q
	160	C ₂₁ H ₂₃ ClN ₄ O ₄	431.0	6.9	32
	161	C ₂₁ H ₂₃ BrClN ₃ O ₂	466.0	7.8	34
10	162	C ₂₁ H ₂₃ ClF ₃ N ₃ O ₂	404.0	13.7	68
	163	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.5	14.6	69
	164	C ₂₁ H ₂₂ Cl ₃ N ₃ O ₂	454.0	17.7	78
15	165	C ₂₁ H ₂₂ BrCl ₄ N ₃ O ₂	454.0	17.2	76
	166	C ₂₂ H ₂₆ ClN ₃ O ₂	400.0	15.0	75
	167	C ₂₃ H ₂₈ ClN ₃ O ₄	443.5	13.9	62
20	168	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	13.7	65
	169	C ₂₁ H ₂₃ BrClN ₃ O ₂	464.0	16.1	69
	170	C ₂₇ H ₂₈ ClN ₃ O ₂	462.0	17.6	76
25	171	C ₂₂ H ₂₃ ClF ₃ N ₃ O ₂	454.0	16.0	71
	172	C ₂₂ H ₂₆ ClN ₃ O ₂	400.0	14.9	75
	173	C ₂₃ H ₂₈ ClN ₃ O ₂	414.0	16.2	78
30	174	C ₂₂ H ₂₃ ClN ₄ O ₂	411.0	14.9	73
	175	C ₂₅ H ₂₆ ClN ₃ O ₂	436.0	17.1	78
	176	C ₂₅ H ₂₆ ClN ₃ O ₂	436.0	13.1	60
35	177	C ₂₁ H ₂₂ ClF ₂ N ₃ O ₂	422.0	14.8	70
	178	C ₂₁ H ₂₂ ClF ₂ N ₃ O ₂	422.0	15.3	73
	179	C ₂₁ H ₂₂ ClF ₂ N ₃ O ₂	422.0	15.3	73
40	180	C ₂₁ H ₂₂ ClF ₂ N ₃ O ₂	422.0	16.4	78
	181	C ₂₃ H ₂₈ ClN ₃ O ₄	443.0	16.9	76
	182	C ₂₂ H ₂₃ ClF ₃ N ₃ O ₂	470.5	12.6	54
45	183	C ₂₂ H ₂₃ ClF ₃ N ₃ O ₂	470.0	20.0	85
	184	C ₂₃ H ₂₆ ClN ₃ O ₄	444.0	17.4	78
	185	C ₂₂ H ₂₂ ClF ₄ N ₃ O ₂	472.0	18.4	78
50	186	C ₂₂ H ₂₂ ClF ₄ N ₃ O ₂	472.0	19.6	83
	187	C ₂₁ H ₂₁ ClF ₃ N ₃ O ₂	440.0	17.0	77
	188	C ₂₁ H ₂₁ ClF ₃ N ₃ O ₂	440.0	17.1	78
55	189	C ₂₃ H ₂₂ ClF ₆ N ₃ O ₂	522.0	20.8	80
	190	C ₂₃ H ₂₂ ClF ₆ N ₃ O ₂	522.0	2.7	10
	191	C ₂₃ H ₂₈ ClN ₃ O ₂	414.0	16.4	79
55	192	C ₂₂ H ₂₃ ClF ₃ N ₃ O ₂	454.0	8.6	38
	193	C ₂₁ H ₂₃ BrClN ₃ O ₂	464.0	11.6	50
	194	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	11.5	55
	195	C ₂₁ H ₂₂ Cl ₃ N ₃ O ₂	454.0	10.0	44
	196	C ₂₂ H ₂₂ ClF ₄ N ₃ O ₂	472.0	10.4	44

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Table 3 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	197	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	8.9	42
	198	C ₂₁ H ₂₄ CIN ₃ O ₂	386.0	10.3	53
	199	C ₂₁ H ₂₃ CIN ₄ O ₄	431.0	14.6	68
10	200	C ₂₂ H ₂₃ ClF ₃ N ₃ O ₂	454.0	10.4	46
	201	C ₂₁ H ₂₃ BrCIN ₃ O ₂	464.0	13.4	58
	202	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	12.7	60
15	203	C ₂₁ H ₂₂ Cl ₃ N ₃ O ₂	454.0	13.2	58
	204	C ₂₂ H ₂₂ ClF ₄ N ₃ O ₂	472.0	12.9	55
	205	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	13.3	63
20	206	C ₂₁ H ₂₄ CIN ₃ O ₂	386.0	24.2	Q
	207	C ₂₁ H ₂₃ CIN ₄ O ₄	431.0	1.0	1
	208	C ₂₃ H ₂₅ ClF ₃ N ₃ O ₂	468.0	15.1	65
25	209	C ₂₂ H ₂₅ BrCIN ₃ O ₂	478.0	18.0	75
	210	C ₂₂ H ₂₅ Cl ₂ N ₃ O ₂	434.0	16.3	75
	211	C ₂₂ H ₂₄ Cl ₃ N ₃ O ₂	468.0	18.6	79
30	212	C ₂₃ H ₂₄ ClF ₄ N ₃ O ₂	486.0	16.5	68
	213	C ₂₂ H ₂₅ Cl ₂ N ₃ O ₂	434.0	14.4	66
	214	C ₂₂ H ₂₆ CIN ₃ O ₂	400.0	14.0	70
35	215	C ₂₂ H ₂₅ CIN ₄ O ₄	445.0	16.8	76
	216	C ₂₆ H ₂₅ ClF ₃ N ₃ O ₂ S	536.0	17.7	66
	217	C ₂₅ H ₂₅ BrCIN ₃ O ₂ S	546.0	20.4	75
40	218	C ₂₅ H ₂₅ Cl ₂ N ₃ O ₂ S	502.0	16.9	67
	219	C ₂₅ H ₂₄ Cl ₃ N ₃ O ₂ S	536.0	18.3	68
	220	C ₂₆ H ₂₄ ClF ₄ N ₃ O ₂ S	554.0	19.4	70
45	221	C ₂₅ H ₂₅ Cl ₂ N ₃ O ₂ S	502.0	19.1	76
	222	C ₂₅ H ₂₆ CIN ₃ O ₂ S	468.0	16.0	68
	223	C ₂₅ H ₂₅ CIN ₄ O ₄ S	513.0	18.4	72
50	224	C ₂₆ H ₂₅ ClF ₃ N ₃ O ₂ S	536.0	13.9	52
	225	C ₂₅ H ₂₅ BrCIN ₃ O ₂ S	546.0	12.9	47
	226	C ₂₅ H ₂₅ Cl ₂ N ₃ O ₂ S	502.0	15.6	62
55	227	C ₂₅ H ₂₄ Cl ₃ N ₃ O ₂ S	536.0	17.3	64
	228	C ₂₆ H ₂₄ ClF ₄ N ₃ O ₂ S	554.0	15.4	56
	229	C ₂₅ H ₂₅ Cl ₂ N ₃ O ₂ S	502.0	13.5	54
55	230	C ₂₅ H ₂₆ CIN ₃ O ₂ S	468.0	13.7	59
	231	C ₂₅ H ₂₅ CIN ₄ O ₄ S	513.0	13.9	54
	232	C ₂₄ H ₂₇ ClF ₃ N ₃ O ₄ S	546.0	10.0	37
55	233	C ₂₃ H ₂₇ BrCIN ₃ O ₄ S	558.0	17.1	61
	234	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₄ S	512.0	17.0	66

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Table 3 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
235	209	C ₂₃ H ₂₆ Cl ₃ N ₃ O ₄ S	546.0	7.3	27
236	210	C ₂₄ H ₂₆ ClF ₄ N ₃ O ₄ S	564.0	19.2	68
237	211	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₄ S	512.0	7.9	31
238	212	C ₂₃ H ₂₈ ClN ₃ O ₄ S	478.0	13.7	57
239	213	C ₂₃ H ₂₇ ClN ₄ O ₄ S	523.0	5.5	21
Note: Q means "Quantitative".					

[Example 240] Synthesis of (R)-3-[N-[3-fluoro-5-(trifluoromethyl)benzoyl]glycyl]amino-1-(3,5-dimethylisoxazol-4-ylmethyl)pyrrolidine (Compd. No. 1191)

[0139] A dichloromethane solution (1 mL) of 3-fluoro-5-(trifluoromethyl)benzoyl chloride (0.058 mmol) was added to a solution of (R)-1-(3,5-dimethylisoxazol-4-ylmethyl)-3-(glycylamino)pyrrolidine (0.050 mmol) and a piperidinomethyl-polystyrene (58 mg) in chloroform (0.2 mL) and dichloromethane (0.75 mL). The reaction mixture was stirred at room temperature for 2 hours, and methanol (1.0 mL) was then added. The resulting mixture was stirred at room temperature for 10 hours. The reaction mixture was loaded onto a VarianTM SCX column and washed with methanol (16 mL). The obtained crude product was eluted with a solution of 2 M NH₃ in methanol (6 mL) and concentrated to provide (R)-3-[N-[3-fluoro-5-(trifluoromethyl)benzoyl]glycyl]amino-1-(3,5-dimethylisoxazol-4-ylmethyl)pyrrolidine (Compd. No. 1191) (19.5 mg, 88%). The purity was determined by RPLC/MS (100%). ESI/MS m/e 443.2 (M⁺+H, C₂₀H₂₂F₄N₄O₃).

[Examples 241 to 265]

[0140] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 240. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 4.

Table 4

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
241	1192	C ₂₀ H ₂₂ F ₄ N ₄ O ₃	443.2	19.2	87
242	1193	C ₂₀ H ₂₃ F ₃ N ₄ O ₄	441.0	17.5	79
243	1194	C ₂₁ H ₂₂ F ₆ N ₄ O ₃	493.0	20.4	83
244	1195	C ₁₉ H ₂₃ BrN ₄ O ₃	435.1	16.8	77
245	1196	C ₁₉ H ₂₃ N ₅ O ₅	402.2	16.2	81
246	1197	C ₂₀ H ₂₂ F ₄ N ₄ O ₃	443.2	17.6	80
247	1198	C ₁₉ H ₂₃ ClN ₄ O ₃	391.0	16.5	84
248	1199	C ₂₀ H ₂₆ N ₄ O ₃	371.0	16.1	87
249	1200	C ₁₉ H ₂₂ Cl ₂ N ₄ O ₃	425.0	18.0	85
250	1201	C ₁₉ H ₂₂ F ₂ N ₄ O ₃	393.0	16.6	85
251	1202	C ₂₀ H ₂₂ F ₄ N ₄ O ₃	443.2	16.8	76
252	1203	C ₂₂ H ₂₄ F ₃ N ₃ O ₃	436.2	17.1	79
253	1204	C ₂₃ H ₂₃ F ₆ N ₃ O ₂	488.2	18.1	74
254	1205	C ₂₁ H ₂₄ BrN ₃ O ₂	430.0	17.5	81
255	1206	C ₂₁ H ₂₄ N ₄ O ₄	397.0	16.2	82
256	1207	C ₂₂ H ₂₃ F ₄ N ₃ O ₂	438.2	17.5	80
257	1208	C ₂₁ H ₂₄ ClN ₃ O ₂	386.0	15.8	82

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Table 4 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
258	1209	C ₂₂ H ₂₇ N ₃ O ₂	366.0	15.7	86
259	1210	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	17.8	85
260	1211	C ₂₁ H ₂₃ F ₂ N ₃ O ₂	388.0	16.3	84
261	1212	C ₂₂ H ₂₃ F ₄ N ₃ O ₂	438.2	17.4	80
262	1213	C ₂₄ H ₂₄ ClF ₆ N ₃ O ₂	536.2	24.0	90
263	1214	C ₂₃ H ₂₄ ClF ₄ N ₃ O ₃	486.2	22.2	91
264	1215	C ₂₂ H ₂₄ Cl ₃ N ₃ O ₂	467.9	20.9	89
265	1216	C ₂₂ H ₂₄ ClF ₂ N ₃ O ₂	436.0	19.3	89

[Example 266] Synthesis of (R)-1-(4-chlorobenzyl)-3-[[N-(4-dimethylaminobenzoyl)glycyl]amino]pyrrolidine (Compd. No. 952)

[0141] Triethylamine (0.021 mL, 0.15 mmol), 4-(dimethylamino)benzoic acid (10 mg, 0.061 mmol), EDCI (10.2 mg, 0.053 mmol) and HOBt (7.5 mg, 0.055 mmol) were added to a chloroform (2 mL) solution of (R)-1-(4-chlorobenzyl)-3-(glycylamino)pyrrolidine (13.8 mg, 0.052 mmol). The resulting reaction mixture was stirred at room temperature for 15 hours. The solution was washed with a 2 M aqueous solution of NaOH (2 mL×2) and brine (2 mL), filtered through a PTFE membrane by using dichloromethane (3 mL), dried and concentrated to thereby afford (R)-1-(4-chlorobenzyl)-3-[[N-(4-dimethylaminobenzoyl)glycyl]amino]pyrrolidine (Compd. No. 952) (24.9 mg). The purity was determined by RPLC/MS (91%). ESI/MS m/e 415.0 (M⁺+H, C₂₂H₂₇ClN₄O₂).

[Examples 267 to 347]

[0142] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 266. The obtained products, if necessary, were purified by solid-phase extraction (Varian™ SCX column) or chromatography (HPLC-C₁₈) to provide the objective compounds. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 5.

Table 5

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
267	951	C ₂₂ H ₂₄ ClN ₃ O ₄	430.0	26.3	Q
268	953	C ₂₃ H ₂₉ ClN ₄ O ₂	429.0	28.8	Q
269	954	C ₂₁ H ₂₅ ClN ₄ O ₂	401.0	27.9	Q
270	955	C ₂₂ H ₂₇ ClN ₄ O ₂	415.0	26.8	Q
271	956	C ₂₁ H ₂₄ ClN ₃ O ₃	402.0	10.3	51
272	957	C ₂₀ H ₂₂ ClN ₃ O ₃	388.0	1.4	7
273	958	C ₂₁ H ₂₄ ClN ₃ O ₃	402.5	1.2	6
274	959	C ₂₂ H ₂₅ ClN ₄ O ₃	429.5	4.7	22
275	960	C ₂₃ H ₂₇ ClN ₄ O ₃	443.0	10.9	49
276	961	C ₂₁ H ₂₅ ClN ₄ O ₂	401.0	28.4	Q
277	962	C ₂₂ H ₂₇ ClN ₄ O ₂	415.0	24.9	Q
278	963	C ₂₁ H ₂₄ ClN ₃ O ₃	402.0	4.4	22
279	964	C ₂₂ H ₂₄ ClN ₃ O ₄	430.0	29.5	Q
280	965	C ₂₃ H ₂₆ ClN ₃ O ₄	444.0	27.2	Q
281	966	C ₂₂ H ₂₄ ClN ₃ O ₃	414.0	27.0	Q

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Table 5 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	282	C ₂₃ H ₂₆ CIN ₃ O ₃	428.0	27.0	Q
	283	C ₂₂ H ₂₃ CIN ₄ O ₂	411.0	21.4	Q
	284	C ₂₃ H ₂₅ CIN ₄ O ₂	425.0	27.6	Q
10	285	C ₂₂ H ₂₇ CIN ₄ O ₂	415.0	28.6	Q
	286	C ₂₃ H ₂₉ CIN ₄ O ₂	429.0	27.9	Q
	287	C ₂₀ H ₂₃ CIN ₄ O ₂	387.0	26.2	Q
15	288	C ₂₁ H ₂₅ CIN ₄ O ₂	401.0	26.8	Q
	289	C ₂₀ H ₂₃ CIN ₄ O ₂	387.0	26.6	Q
	290	C ₂₁ H ₂₅ CIN ₄ O ₂	401.0	28.2	Q
20	291	C ₂₂ H ₂₃ CIN ₄ O ₂	411.0	29.2	Q
	292	C ₂₃ H ₂₅ CIN ₄ O ₂	425.0	29.5	Q
	293	C ₂₀ H ₂₁ CIN ₆ O ₂	413.0	2.2	11
25	294	C ₂₁ H ₂₃ CIN ₆ O ₂	427.0	10.2	48
	295	C ₂₂ H ₂₅ CIN ₄ O ₃	429.0	28.8	Q
	296	C ₂₃ H ₂₇ CIN ₄ O ₃	443.0	11.9	54
30	297	C ₂₂ H ₂₇ CIN ₄ O ₂	415.0	27.4	Q
	298	C ₂₃ H ₂₉ CIN ₄ O ₂	429.5	28.1	Q
	299	C ₂₁ H ₂₄ CIN ₃ O ₃	402.0	27.7	Q
35	300	C ₂₂ H ₂₆ CIN ₃ O ₃	416.0	28.6	Q
	301	C ₂₁ H ₂₈ N ₄ O ₄	401	15.5*	38
	302	C ₂₁ H ₂₈ N ₄ O ₃	385	10.9*	28
40	303	C ₂₁ H ₂₅ F ₃ N ₄ O ₃	439	17.3*	39
	304	C ₂₁ H ₂₄ FN ₅ O ₃	415	12.7*	30
	305	C ₂₁ H ₂₄ CIN ₅ O ₃	430	17.5*	41
45	306	C ₂₂ H ₂₇ N ₅ O ₃	410	20.6*	50
	307	C ₁₉ H ₂₃ F ₃ N ₄ O ₄	429	13.8*	32
	308	C ₂₁ H ₃₀ N ₄ O ₄	403	17.7*	43
50	309	C ₁₈ H ₂₄ N ₄ O ₃ S ₂	409	12.6*	30
	310	C ₁₉ H ₂₃ Cl ₂ N ₅ O ₃	440	16.9*	38
	311	C ₂₂ H ₃₁ N ₅ O ₆	462	38.6*	85
55	312	C ₂₀ H ₂₆ BrN ₅ O ₃	464	20.4	45
	313	C ₂₀ H ₂₇ N ₅ O ₄	403	5.8*	14
	314	C ₂₁ H ₂₉ N ₅ O ₃	400	6.9*	17
	315	C ₂₄ H ₂₈ N ₄ O ₂	405	22.4	68
	316	C ₂₂ H ₂₇ BrN ₄ O ₂	461	23.8	15
	317	C ₂₂ H ₂₃ F ₄ N ₃ O ₂	438	20.9	59

Note: * indicated "yield (mg) of trifluoroacetate".
Q means "Quantitative".

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Table 5 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
318	1294	C ₂₂ H ₂₃ F ₄ N ₃ O ₂	438	20.8	59
319	1295	C ₂₃ H ₃₁ N ₃ O ₃	398	17.5	54
320	1296	C ₂₀ H ₂₅ N ₃ O ₂ S ₂	404	18.8	58
321	1297	C ₂₁ H ₂₄ F ₃ N ₃ O ₃	424	18.1	53
322	1388	C ₂₁ H ₃₂ N ₆ O ₃	417	7.4*	24
323	1389	C ₁₉ H ₂₂ N ₆ O ₄	399	15.2	48
324	1401	C ₂₃ H ₂₅ ClN ₄ O ₂	425	8.3*	16
325	1402	C ₂₄ H ₃₂ N ₄ O ₅	457	8.3*	15
326	1403	C ₂₀ H ₂₄ N ₄ O ₂	353	14.8	52
327	1404	C ₂₀ H ₂₄ N ₄ O ₂	353	17.0	60
328	1405	C ₂₁ H ₂₆ N ₄ O ₂ S	399	17.3	54
329	1407	C ₂₂ H ₂₈ N ₄ O ₂ S	413	19.1	57
330	1410	C ₁₉ H ₂₄ N ₄ O ₃	357	9.7*	59
331	1769	C ₂₂ H ₂₆ ClF ₃ N ₄ O ₅	519	11.6*	20
332	1770	C ₂₆ H ₂₈ Cl ₂ N ₆ O ₄	559	13.1*	21
333	1771	C ₂₆ H ₃₇ N ₅ O ₄	484	12.7*	23
334	1772	C ₂₈ H ₃₉ N ₅ O ₄	510	5.5*	9
335	1773	C ₂₈ H ₃₇ N ₅ O ₄	509	6.2*	11
336	1774	C ₂₈ H ₃₄ N ₆ O ₆	551	13.6*	22
337	2039	C ₁₉ H ₂₄ N ₄ O ₂	341	5.2*	14
338	2040	C ₂₂ H ₂₇ N ₃ O ₄	398	2.0*	5
339	2041	C ₂₃ H ₂₉ N ₃ O ₃	396	6.2*	15
340	2042	C ₂₅ H ₃₇ N ₃ O ₂	413	2.6*	6
341	2043	C ₂₄ H ₃₁ N ₃ O ₂	394	6.8*	17
342	2044	C ₂₅ H ₂₈ N ₄ O ₄	449	8.7*	16
343	2045	C ₂₆ H ₂₉ ClN ₆ O ₄	525	11.4*	19
344	2046	C ₂₇ H ₃₂ N ₆ O ₄	505	7.7*	13
345	2047	C ₂₈ H ₃₂ N ₄ O ₄	489	10.0*	18
346	2048	C ₂₈ H ₃₇ N ₅ O ₅	524	3.7*	6
347	2049	C ₂₈ H ₃₇ N ₅ O ₄	509	5.3*	9

Note: * indicated "yield (mg) of trifluoroacetate".
Q means "Quantitative".

[Example 348] Synthesis of (R)-1-(4-chlorobenzyl)-3-[[N-(2-amino-5-chlorobenzoyl)glycyl]amino]pyrrolidine (Compd. No. 1084)

[0143] 2-Amino-5-chlorobenzoic acid (0.060 mL) and diisopropylcarbodiimide (0.060 mol) were added to a chloroform (2 mL) solution of (R)-1-(4-chlorobenzyl)-3-(glycylamino)pyrrolidine (0.050 mmol). The resulting reaction solution was stirred at room temperature for 15 hours. The mixture solution was loaded onto a Varian™ SCX column and washed with methanol (15 mL). The obtained crude product was eluted with a solution of 2 M NH₃ in methanol (5 mL) and concentrated to thereby afford (R)-1-(4-chlorobenzyl)-3-[N-[2-amino-5-chlorobenzoyl]glycyl]amino]pyrrolidine

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(Compd. No. 1084) (12.7 mg, 60%). The purity was determined by RPLC/MS (87%). ESI/MS m/e 421.0 (M⁺+H, C₂₀H₂₂Cl₂N₄O₂).

[Examples 349 to 361]

[0144] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 348. When the starting amine remained, a chloroform (1 mL) solution of an isocyanatomethylated polystyrene (50 mg) was added and reacted at room temperature. The resulting reaction mixtures were filtered and concentrated to thereby afford the objective compounds. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 6.

Table 6

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
349	1085	C ₂₀ H ₂₂ ClN ₅ O ₄	432.0	4.1	19
350	1086	C ₂₀ H ₂₃ ClN ₄ O ₂	387.0	7.9	41
351	1087	C ₂₂ H ₂₃ ClN ₄ O ₂	411.0	15.0	73
352	1088	C ₁₈ H ₂₀ ClN ₃ O ₃	362.0	12.9	71
353	1089	C ₂₂ H ₂₂ ClFN ₄ O ₂	429.0	16.0	75
354	1090	C ₂₂ H ₂₆ ClN ₃ O ₃	416.0	15.8	76
355	1091	C ₂₁ H ₂₄ Cl ₂ N ₄ O ₂	435.0	10.9	50
356	1092	C ₂₁ H ₂₄ ClN ₅ O ₄	446.0	7.9	35
357	1093	C ₂₁ H ₂₅ ClN ₄ O ₂	401.0	9.5	47
358	1094	C ₂₃ H ₂₅ ClN ₄ O ₂	425.0	15.8	74
359	1095	C ₁₉ H ₂₂ ClN ₃ O ₃	376.0	13.5	72
360	1096	C ₂₃ H ₂₄ ClFN ₄ O ₂	443.0	11.8	53
361	1097	C ₂₃ H ₂₈ ClN ₃ O ₃	430.0	15.1	70

[Example 362] Synthesis of (R)-1-(4-chlorobenzyl)-3-[[N-(3-bromo-4-methylbenzoyl)glycyl]amino]pyrrolidine (Compd. No. 1098)

[0145] 3-Bromo-4-methylbenzoic acid (0.060 mL), diisopropylcarbodiimide (0.060 mmol) and HOBt (0.060 mmol) were added to a solution of (R)-1-(4-chlorobenzyl)-3-(glycylamino)pyrrolidine (0.050 mmol) in chloroform (1.35 mL) and tert-butanol (0.15 mL). The resulting reaction mixture was stirred at room temperature for 15 hours. The mixture solution was loaded onto a VarianTM SCX column and washed with methanol/chloroform =1:1 (12 mL) and methanol (12 mL). The crude product was eluted with a solution of 2 M NH₃ in methanol (5 mL) and concentrated to thereby provide (R)-1-(4-chlorobenzyl)-3-[[N-(3-bromo-4-methylbenzoyl)glycyl]amino]pyrrolidine (Compd. No. 1098) (11.6 mg, 50%). The purity was determined by RPLC/MS (94%). ESI/MS m/e 466.0 (M⁺+H, C₂₁H₂₃BrClN₃O₂).

[Examples 363 to 572]

[0146] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 362. The obtained products, if necessary, were purified by preparative TLC to afford the objective compounds. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 7.

[0147] The following three compounds were obtained as by-products of the Compd. Nos. 1415, 1416 and 1417.

[0148] Compd. No. 1419: 7.9 mg, yield 38%, ESI/MS m/e 419.0 (C₂₀H₂₃ClN₄O₂S).

[0149] Compd. No. 1420: 7.1 mg, yield 36%, ESI/MS m/e 399.2 (C₂₃H₂₆N₄O₂S).

[0150] Compd. No. 1421: 7.4 mg, yield 37%, ESI/MS m/e 404.2 (C₁₉H₂₅N₅O₃S).

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Table 7

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	363	C ₂₀ H ₂₀ BrClFN ₃ O ₂	470.0	3.1	13
	364	C ₂₀ H ₂₀ Cl ₂ FN ₃ O ₂	424.0	3.1	15
	365	C ₂₁ H ₂₃ ClIN ₃ O ₂	512.0	12.5	49
	366	C ₂₁ H ₂₃ CIN ₄ O ₄	431.2	7.7	36
10	367	C ₂₂ H ₂₆ BrN ₃ O ₂	446.0	13.8	62
	368	C ₂₁ H ₂₃ BrFN ₃ O ₂	450.0	16.5	74
	369	C ₂₁ H ₂₃ ClFN ₃ O ₂	404.2	14.7	73
15	370	C ₂₂ H ₂₆ IN ₃ O ₂	492.0	18.5	75
	371	C ₂₂ H ₂₆ N ₄ O ₄	411.2	15.2	74
	372	C ₂₀ H ₂₅ BrN ₄ O ₃	449.0	12.8	57
	373	C ₁₉ H ₂₂ BrFN ₄ O ₃	455.0	16.2	71
20	374	C ₁₉ H ₂₂ ClFN ₄ O ₃	409.2	14.4	70
	375	C ₂₀ H ₂₅ IN ₄ O ₃	497.0	17.9	72
	376	C ₂₀ H ₂₅ N ₅ O ₅	416.2	14.9	72
25	377	C ₂₃ H ₂₇ BrCIN ₃ O ₂	494.0	16.1	65
	378	C ₂₂ H ₂₄ BrClFN ₃ O ₂	498.0	20.2	81
	379	C ₂₂ H ₂₄ Cl ₂ FN ₃ O ₂	452.2	18.6	82
	380	C ₂₃ H ₂₇ ClIN ₃ O ₂	539.1	21.9	81
30	381	C ₂₃ H ₂₇ CIN ₄ O ₄	459.2	18.7	81
	382	C ₂₁ H ₂₃ BrCIN ₃ O ₂	466.0	4.9	21
	383	C ₂₂ H ₂₃ CIN ₄ O ₃	427.2	16.1	75
35	384	C ₂₃ H ₂₅ CIN ₄ O ₃	441.2	22.8	Q
	385	C ₂₀ H ₂₂ ClFN ₄ O ₂	405.2	21.4	Q
	386	C ₂₂ H ₂₆ BrN ₃ O ₂	446.0	15.8	71
	387	C ₂₃ H ₂₆ N ₄ O ₃	407.2	17.6	87
40	388	C ₂₄ H ₂₈ N ₄ O ₃	421.2	20.2	96
	389	C ₂₁ H ₂₅ FN ₄ O ₂	385.0	16.2	84
	390	C ₂₁ H ₂₅ N ₅ O ₄	412.2	2.3	11
45	391	C ₂₃ H ₂₆ N ₄ O ₂	391.0	21.6	Q
	392	C ₂₀ H ₂₅ BrN ₄ O ₃	451.0	20.1	89
	393	C ₂₁ H ₂₆ N ₅ O ₄	412.2	13.3	65
	394	C ₂₂ H ₂₇ N ₅ O ₄	426.2	20.9	98
50	395	C ₁₉ H ₂₄ FN ₅ O ₃	390.0	20.0	Q
	396	C ₁₉ H ₂₄ N ₆ O ₅	417.2	18.2	87
	397	C ₂₁ H ₂₅ N ₅ O ₃	396.2	17.6	89
55	398	C ₂₃ H ₂₇ BrCIN ₃ O ₂	494.0	22.1	90
	399	C ₂₄ H ₂₇ CIN ₄ O ₃	455.2	17.2	76

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Table 7 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	400	C ₂₅ H ₂₉ ClN ₄ O ₃	469.2	21.1	90
	401	C ₂₂ H ₂₆ ClFN ₄ O ₂	433.2	20.4	94
	402	C ₂₁ H ₂₀ Cl ₂ F ₃ N ₃ O ₂	474.0	38.5	81
10	403	C ₂₁ H ₂₃ ClFN ₃ O ₂	404.2	35.6	88
	404	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	3.7	9
	405	C ₂₀ H ₂₂ ClIN ₄ O ₂	513.0	53.0	Q
15	406	C ₂₀ H ₂₁ ClF ₂ N ₄ O ₂	423.0	38.7	92
	407	C ₁₉ H ₂₃ ClN ₄ O ₂	375.2	33.6	90
	408	C ₂₆ H ₂₆ ClN ₃ O ₂ S	496.0	43.7	88
20	409	C ₂₀ H ₂₁ ClN ₄ O ₅	433.0	40.6	94
	410	C ₂₂ H ₂₃ ClF ₃ N ₃ O ₂	454.2	18.4	41
	411	C ₂₂ H ₂₆ FN ₃ O ₂	384.0	17.1	45
25	412	C ₂₂ H ₂₆ ClN ₃ O ₂	400.2	17.5	44
	413	C ₂₁ H ₂₅ IN ₄ O ₂	493.0	23.3	47
	414	C ₂₁ H ₂₄ F ₂ N ₄ O ₂	403.2	18.4	46
30	415	C ₂₀ H ₂₆ N ₄ O ₂	355.2	15.7	44
	416	C ₂₇ H ₂₉ N ₃ O ₂ S	476.0	20.9	88
	417	C ₂₁ H ₂₄ N ₄ O ₅	413.0	19.9	96
35	418	C ₂₀ H ₂₂ ClF ₃ N ₄ O ₃	459.0	19.4	85
	419	C ₂₀ H ₂₅ FN ₄ O ₃	389.0	17.8	92
	420	C ₂₀ H ₂₅ ClN ₄ O ₃	405.2	18.7	92
40	421	C ₁₉ H ₂₄ IN ₅ O ₃	498.0	23.9	96
	422	C ₁₉ H ₂₃ F ₂ N ₅ O ₃	408.2	19.0	93
	423	C ₁₈ H ₂₅ N ₅ O ₃	360.0	16.3	91
45	424	C ₂₅ H ₂₈ N ₄ O ₃ S	481.2	21.4	89
	425	C ₁₉ H ₂₃ N ₅ O ₆	418.0	19.9	95
	426	C ₂₃ H ₂₄ Cl ₂ F ₃ N ₃ O ₂	502.0	22.5	90
50	427	C ₂₃ H ₂₇ ClFN ₃ O ₂	432.2	21.2	98
	428	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₂	448.0	21.6	96
	429	C ₂₂ H ₂₆ ClIN ₄ O ₂	541.0	26.4	98
55	430	C ₂₂ H ₂₅ ClF ₂ N ₄ O ₂	451.0	21.3	94
	431	C ₂₁ H ₂₇ ClN ₄ O ₂	403.2	19.4	96
	432	C ₂₈ H ₃₀ ClN ₃ O ₂ S	524.0	24.7	94
55	433	C ₂₂ H ₂₅ ClN ₄ O ₅	461.0	20.7	90
	434	C ₂₀ H ₂₀ Cl ₂ N ₄ O ₄	451.0	7.4	33
	435	C ₂₁ H ₂₃ ClN ₄ O ₄	431.2	15.5	72
	436	C ₁₉ H ₂₂ ClN ₅ O ₅	436.0	22.9	Q
	437	C ₂₃ H ₂₈ ClN ₃ O ₂	414.2	17.9	86

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Table 7 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	438	C ₂₄ H ₃₁ N ₃ O ₂	394.2	15.8	80
	439	C ₂₂ H ₃₀ N ₄ O ₃	399.2	17.3	87
	440	C ₂₀ H ₂₂ BrClN ₄ O ₂	467.0	21.3	91
10	441	C ₂₁ H ₂₅ BrN ₄ O ₂	445.0	20.7	93
	442	C ₁₉ H ₂₄ BrN ₅ O ₃	450.0	21.8	97
	443	C ₂₁ H ₂₅ ClN ₄ O ₂	401.2	18.1	90
15	444	C ₁₉ H ₂₄ ClN ₅ O ₃	406.0	20.1	99
	445	C ₂₃ H ₂₉ N ₃ O ₃	396.2	16.8	85
	446	C ₂₃ H ₃₀ ClN ₃ O ₃	432.2	19.8	92
20	447	C ₂₄ H ₃₃ N ₃ O ₃	412.2	17.4	85
	448	C ₂₂ H ₃₂ N ₄ O ₄	417.2	18.7	90
	449	C ₂₅ H ₂₆ ClN ₃ O ₃	452.2	29.1	Q
25	450	C ₂₆ H ₂₉ N ₃ O ₃	432.2	18.1	84
	451	C ₂₄ H ₂₈ N ₄ O ₄	437.2	19.3	88
	452	C ₂₃ H ₂₂ ClF ₃ N ₄ O ₃	495.2	20.6	83
30	453	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₃	436.0	17.5	80
	454	C ₂₀ H ₂₁ BrClN ₃ O ₃	468.0	19.2	82
	455	C ₂₀ H ₂₁ Cl ₂ N ₃ O ₃	422.2	17.3	82
35	456	C ₂₀ H ₂₀ ClFN ₄ O ₄	435.0	17.1	79
	457	C ₂₄ H ₂₅ F ₃ N ₄ O ₃	475.2	21.7	91
	458	C ₂₂ H ₂₆ ClN ₃ O ₃	416.2	17.8	86
40	459	C ₂₁ H ₂₄ BrN ₃ O ₃	448.0	19.5	87
	460	C ₂₁ H ₂₄ ClN ₃ O ₃	402.2	16.7	83
	461	C ₂₁ H ₂₃ FN ₄ O ₄	415.2	18.1	87
45	462	C ₂₂ H ₂₄ F ₃ N ₅ O ₄	480.2	20.3	85
	463	C ₂₀ H ₂₅ ClN ₄ O ₄	421.2	18.6	88
	464	C ₁₉ H ₂₃ BrN ₄ O ₄	451.0	21.3	94
50	465	C ₁₉ H ₂₃ ClN ₄ O ₄	407.2	19.1	94
	466	C ₁₉ H ₂₂ FN ₅ O ₅	420.2	19.1	91
	467	C ₂₅ H ₂₆ ClF ₃ N ₄ O ₃	523.2	25.0	96
55	468	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₃	464.2	12.2	53
	469	C ₂₂ H ₂₅ BrClN ₃ O ₃	496.0	24.1	97
	470	C ₂₂ H ₂₅ Cl ₂ N ₃ O ₃	450.2	21.8	97
	471	C ₂₀ H ₂₀ BrCl ₂ N ₃ O ₂	486.0	5.1	21
	472	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	10.5	50
	473	C ₂₀ H ₂₀ Cl ₂ IN ₃ O ₂	532.0	7.1	27
	474	C ₂₁ H ₂₄ ClN ₃ O ₃	402.2	22.2	Q
	475	C ₂₇ H ₂₆ ClN ₃ O ₃	476.0	22.2	93

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Table 7 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	476	C ₂₀ H ₂₁ ClIN ₃ O ₃	514.0	26.9	Q
	477	C ₂₁ H ₂₅ ClN ₄ O ₂	401.2	24.2	Q
	478	C ₂₁ H ₂₃ BrClN ₃ O ₂	466.0	23.1	99
10	479	C ₂₂ H ₂₆ ClN ₃ O ₂	400.2	16.4	82
	480	C ₂₁ H ₂₃ ClIN ₃ O ₂	512.2	20.8	81
	481	C ₂₁ H ₂₄ N ₃ O ₃	382.2	19.6	Q
15	482	C ₂₈ H ₂₉ N ₃ O ₃	456.2	21.1	93
	483	C ₂₁ H ₂₄ IN ₃ O ₃	494.0	25.3	Q
	484	C ₂₂ H ₂₈ N ₄ O ₂	381.2	19.0	Q
20	485	C ₁₉ H ₂₂ BrClN ₄ O ₃	471.0	25.8	Q
	486	C ₂₀ H ₂₅ ClN ₄ O ₃	405.2	18.5	91
	487	C ₁₉ H ₂₂ ClIN ₄ O ₃	517.0	23.1	89
25	488	C ₂₀ H ₂₆ N ₄ O ₄	387.2	20.6	Q
	489	C ₂₆ H ₂₈ N ₄ O ₄	461.2	23.7	Q
	490	C ₁₉ H ₂₃ IN ₄ O ₄	499.0	28.2	Q
30	491	C ₂₀ H ₂₆ N ₄ O ₄	386.0	20.5	Q
	492	C ₂₂ H ₂₄ BrCl ₂ N ₃ O ₂	514.0	27.2	Q
	493	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₂	448.0	21.4	95
35	494	C ₂₂ H ₂₄ Cl ₂ IN ₃ O ₂	560.0	27.0	96
	495	C ₂₃ H ₂₈ ClN ₃ O ₃	430.2	23.8	Q
	496	C ₂₂ H ₂₅ ClIN ₃ O ₃	542.0	29.4	Q
40	497	C ₁₉ H ₂₂ ClN ₃ O ₂ S	392.0	16.9	43
	498	C ₂₀ H ₂₅ N ₃ O ₂ S	372.2	6.9	19
	499	C ₁₈ H ₂₄ N ₄ O ₃ S	377.2	8.1	43
45	500	C ₂₁ H ₂₆ ClN ₃ O ₂ S	420.0	13.0	62
	501	C ₂₂ H ₂₄ BrClN ₄ O ₃	509.2	5.0	10
	502	C ₂₃ H ₂₇ BrN ₄ O ₃	489.2	3.6	15
50	503	C ₂₁ H ₂₆ BrN ₅ O ₄	494.0	2.8	11
	504	C ₂₄ H ₂₈ BrClN ₄ O ₃	537.2	5.2	19
	505	C ₂₁ H ₂₂ ClN ₅ O ₂	412.0	25.5	Q
55	506	C ₂₂ H ₂₅ N ₅ O ₂	392.0	16.5	84
	507	C ₂₀ H ₂₄ N ₆ O ₃	397.2	19.9	Q
	508	C ₂₃ H ₂₆ ClN ₅ O ₂	440.2	21.8	99
55	509	C ₂₁ H ₂₀ Cl ₂ F ₃ N ₃ O ₂	474.0	18.4	78
	510	C ₂₄ H ₂₄ ClF ₆ IN ₃ O ₄	568.0	24.1	85
	511	C ₁₈ H ₁₉ BrClN ₃ O ₂ S	458.0	19.4	85
55	512	C ₂₆ H ₂₆ ClN ₃ O ₄ S	512.2	22.1	86
	513	C ₂₆ H ₂₆ ClN ₃ O ₂	448.0	19.1	85

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Table 7 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	514	C ₂₂ H ₂₃ ClF ₃ N ₃ O ₂	454.2	16.2	71
	515	C ₂₅ H ₂₇ F ₆ IN ₃ O ₄	548.2	22.1	81
	516	C ₁₉ H ₂₂ BrN ₃ O ₂ S	436.0	17.1	78
10	517	C ₂₇ H ₂₉ N ₃ O ₄ S	492.0	19.4	79
	518	C ₂₇ H ₂₉ N ₃ O ₂	428.2	18.1	85
	519	C ₂₀ H ₂₂ ClF ₃ N ₄ O ₃	459.0	17.3	75
15	520	C ₂₃ H ₂₆ F ₆ IN ₄ O ₅	553.2	21.0	76
	521	C ₁₇ H ₂₁ BrN ₄ O ₃ S	443.0	16.4	74
	522	C ₂₅ H ₂₈ N ₄ O ₅ S	497.0	18.4	74
20	523	C ₂₅ H ₂₈ N ₄ O ₃	433.2	17.3	80
	524	C ₂₃ H ₂₄ Cl ₂ F ₃ N ₃ O ₂	502.0	20.0	80
	525	C ₂₀ H ₂₃ BrClN ₃ O ₂ S	486.0	21.0	87
25	526	C ₂₈ H ₃₀ ClN ₃ O ₄ S	540.2	23.8	88
	527	C ₂₈ H ₃₀ ClN ₃ O ₂	476.0	20.0	84
	528	C ₂₂ H ₂₄ Cl ₂ N ₄ O ₃	463.0	0.4	2
30	529	C ₂₃ H ₂₇ ClN ₄ O ₂	443.0	1.3	6
	530	C ₂₁ H ₂₆ ClN ₅ O ₄	448.0	1.1	5
	531	C ₂₄ H ₂₈ Cl ₂ N ₄ O ₃	491.0	0.8	3
35	532	C ₂₁ H ₂₂ ClN ₅ O ₂ S	444.0	6.8	31
	533	C ₂₂ H ₂₅ N ₅ O ₂ S	424.0	4.8	23
	534	C ₂₀ H ₂₄ N ₆ O ₃ S	429.2	4.5	21
40	535	C ₂₃ H ₂₆ ClN ₅ O ₂ S	472.0	10.4	44
	536	C ₂₇ H ₂₆ ClN ₃ O ₃	476.0	23.9	Q
	537	C ₂₇ H ₂₉ N ₃ O ₄ S	456.2	28.0	Q
45	538	C ₂₆ H ₂₈ N ₄ O ₄	461.2	22.3	97
	539	C ₂₉ H ₃₀ ClN ₃ O ₃	504.2	26.8	Q
	540	C ₂₁ H ₂₂ ClF ₃ N ₄ O ₂	455.0	14.6	64
50	541	C ₂₁ H ₂₂ ClF ₃ N ₄ O ₃	471.0	17.4	74
	542	C ₁₉ H ₂₀ BrClN ₄ O ₂	453.0	15.6	69
	543	C ₁₉ H ₂₀ Cl ₂ N ₄ O ₂	407.2	2.3	11
55	544	C ₂₆ H ₂₆ ClN ₃ O ₃	464.0	15.4	66
	545	C ₂₀ H ₂₃ ClN ₄ O ₂	387.0	14.8	77
	546	C ₂₂ H ₂₅ F ₃ N ₄ O ₂	435.2	11.1	51
	547	C ₂₀ H ₂₅ F ₃ N ₄ O ₃	451.2	16.3	72
	548	C ₂₀ H ₂₃ BrN ₄ O ₂	433.0	15.4	71
	549	C ₂₀ H ₂₃ ClN ₄ O ₂	387.0	15.6	81
	550	C ₂₇ H ₂₉ N ₃ O ₃	444.2	14.8	67
	551	C ₂₀ H ₂₄ F ₃ N ₅ O ₃	440.2	16.2	74

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Table 7 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
552	1595	C ₂₀ H ₂₄ F ₃ N ₅ O ₄	456.2	15.4	68
553	1596	C ₁₈ H ₂₂ BrN ₅ O ₃	436.0	15.6	72
554	1597	C ₁₈ H ₂₂ ClN ₅ O ₃	391.8	14.4	73
555	1598	C ₂₅ H ₂₈ N ₄ O ₄	449.2	15.9	71
556	1599	C ₁₉ H ₂₅ N ₅ O ₃	372.2	15.8	85
557	1606	C ₂₁ H ₂₁ ClF ₃ N ₃ O ₂ S	472.0	17.0	72
558	1607	C ₂₁ H ₂₁ ClF ₃ N ₃ O ₂ S	452.2	15.3	68
559	1608	C ₂₀ H ₂₃ F ₃ N ₄ O ₃ S	457.2	15.9	70
560	1660	C ₂₁ H ₂₂ BrF ₃ N ₄ O ₂	501.0	19.0	76
561	1661	C ₂₁ H ₂₂ BrF ₃ N ₄ O ₃	517.0	16.2	63
562	1662	C ₂₀ H ₂₁ BrF ₂ N ₄ O ₂	469.0	15.1	65
563	1663	C ₂₀ H ₂₂ BrClN ₄ O ₂	467.0	14.5	62
564	1692	C ₂₀ H ₂₃ Br ₂ N ₃ O ₃	514	7.3	28
565	1693	C ₂₂ H ₂₆ F ₂ N ₄ O ₂	417	16.2	78
566	1694	C ₂₂ H ₂₇ FN ₄ O ₂	399	21.8	Q
567	1695	C ₂₂ H ₂₇ BrN ₄ O ₂	459	24.5	Q
568	1696	C ₂₂ H ₂₇ IN ₄ O ₂	507	27.4	Q
569	1697	C ₂₂ H ₂₇ ClN ₄ O ₂	415	22.1	Q
570	1698	C ₂₃ H ₂₇ F ₃ N ₄ O ₃	465	24.3	Q
571	1699	C ₂₃ H ₂₇ F ₃ N ₄ O ₂	449	25.3	Q
572	1700	C ₂₂ H ₂₅ BrClN ₃ O ₂	480	17.8	74
Note: Q means "Quantitative".					

[0151] For example, Compd. No. 1583 exhibited the following NMR: ¹H NMR (400MHz, CD₃OD) δ 1.64-1.72 (m, 1 H), 2.20-2.30 (m, 1 H), 2.41-2.51 (m, 2 H), 2.71-2.78 (m, 2 H), 3.59 (dd, J = 15.4, 12.9 Hz, 2 H), 3.94 (s, 2 H), 4.35-4.41 (m, 1 H), 6.82 (d, J = 8.6 Hz, 1 H), 7.29 (s, 4 H), 7.40 (dd, J = 8.6, 1.7 Hz, 1 H), 7.85 (d, J = 0.96 Hz, 1 H).

[Reference Example 4] Synthesis of (S)-3-[N-[3-(trifluoromethyl)benzoyl]glycyl]aminopyrrolidine

[0152] A suspension of (S)-1-(4-chlorobenzyl)-3-[N-[3-(trifluoromethyl)benzoyl]glycyl]aminopyrrolidine (2.93 g, 6.66 mmol) and Pd(OH)₂ in a 5% formic acid/methanol (70 mL) was stirred at 60 °C for 3 hours. The palladium catalyst was removed by filtration through Celite to concentrate the filtrate. A 2 M solution of NaOH (100 mL) was added to the resulting residue, and the resulting mixture was extracted with ethyl acetate (100mL×3). The extracts were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, concentrated and purified by column chromatography [SiO₂, ethyl acetate/methanol/triethylamine = (85:10:5) to (60:30:5)] to thereby provide (S)-3-[N-3-(trifluoromethyl)benzoyl]glycyl]aminopyrrolidine (1.70 g, 81%) as an oil. ¹H NMR (CDCl₃, 270MHz) δ 1.76 (d, J = 7.3 Hz, 1 H), 2.07-2.25 (m, 1 H), 2.81-2.98 (m, 2 H), 3.02-3.11 (m, 2 H), 4.12 (s, 2 H), 4.41 (br, 1 H), 6.90 (br, 1 H), 7.45 (br, 1 H), 7.58 (dd, J = 7.3 and 7.3 Hz, 1 H), 7.77 (d, J = 7.3 Hz, 1 H), 8.02 (d, J = 7.3 Hz, 1 H), 8.11 (s, 1 H); ESI/MS m/e 316.0 (M⁺+H, C₁₄H₁₆F₃N₃O₂).

[0153] Further, (R)-3-[N-[3-(trifluoromethyl)benzoyl]glycyl]aminopyrrolidine was synthesized by using the corresponding starting material and reactants according to the above method. 1.49 g, 68%. The product exhibited the same ¹H NMR and ESI/MS as those of the (S)-isomer.

[0154] In addition, (R)-3-[N-[2-amino-5-(trifluoromethyl)benzoyl]glycyl]aminopyrrolidine was synthesized by using the corresponding starting material and reactants according to the above method. 316 mg, 93%; ESI/MS m/e 331.2 (M⁺+H, C₁₄H₁₇F₃N₄O₂).

[0155] Moreover, (R)-3-[N-[2-(tert-butoxycarbonylamino)-5-(trifluoromethoxy)benzoyl]glycyl]aminopyrrolidine was synthesized by using the corresponding starting material and reactants according to the above method. Quantitative yield; ¹H NMR (CDCl₃, 400MHz) δ 1.51 (s, 9 H), 1.60-1.70 (m, 2 H), 2.10-2.25 (m, 1 H), 2.80-2.88 (m, 1 H), 2.89-2.98 (m, 1 H), 3.04-3.18 (m, 2 H), 4.05 (d, J = 4.9 Hz, 2 H), 4.43 (br, 1 H), 6.15 (br, 1 H), 7.03 (br, 1 H), 7.32 (d, J = 9.3 Hz, 1 H), 7.38 (s, 1 H), 8.42 (d, J = 9.3 Hz, 1 H).

[Example 573] Synthesis of (R)-3-[[N-[2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl]glycyl]amino]-1-(4-chlorobenzyl)pyrrolidine

[0156] Triethylamine (2.9 mL, 20.5 mmol), 2-(tert-butoxycarbonylamino)-5-(trifluoromethyl)benzoic acid (6.27 g, 20.5 mmol), EDCI (3.9 g, 20.5 mmol) and HOBt (2.8 g, 20.5 mmol) were added to a dichloromethane (100 mL) solution of (R)-1-(4-chlorobenzyl)-3-(glycylamino)pyrrolidine (5.0 g, 18.7 mmol). The resulting reaction mixture was stirred at room temperature overnight. A 2 M aqueous solution (80 mL) of NaOH was added to the reaction mixture, and the resulting mixture was extracted with dichloromethane. The obtained extract was dried over anhydrous Na₂SO₄, filtered, concentrated and purified by column chromatography [SiO₂, hexane/ethyl acetate = (1:1) to (1:4)] to thereby afford (R)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]-1-(4-chlorobenzyl)pyrrolidine (9.41 g, 91%) as a white amorphous solid. ESI/MS m/e 555.2 (M⁺+H, C₂₆H₃₀ClF₃N₄O₄).

[Reference Example 5] Synthesis of (R)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine

[0157] A mixture of (R)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]-1-(4-chlorobenzyl)pyrrolidine (6.3 g, 11.4 mmol) with Pd(OH)₂ (1.68 g), formic acid (3.7 mL) and methanol (80 mL) was stirred at 50 °C overnight. The mixture was cooled to room temperature, and the palladium catalyst was then removed by filtration through Celite. The resulting filtrate was concentrated and purified by column chromatography [SiO₂, ethyl acetate/methanol = (5:1) to (4:1)] to thereby provide (R)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (4.42 g, 90%) as a white solid. ¹H NMR (CDCl₃, 400MHz) δ 1.48 (s, 9 H), 2.0-2.4 (m, 2 H), 3.42-3.71 (m, 5 H), 4.00-4.22 (m, 2 H), 4.56 (br, 1 H), 7.48 (d, J = 9.0 Hz, 1 H), 7.93 (s, 1 H), 8.17 (br, 1 H), 8.33 (d, J = 9.0 Hz, 1 H), 8.45 (br, 1 H).

[Example 574] Synthesis of (S)-1-benzyl-3-[N-[3-(trifluoromethyl)benzoyl]glycyl]aminopyrrolidine (Compd. No. 239)

[0158] An acetonitrile (1.1 mL) solution of (S)-3-[N-[3-(trifluoromethyl)benzoyl]glycyl]aminopyrrolidine (0.06 mmol) and a (piperidinomethyl)polystyrene (2.6 to 2.8 mmol/g, 30 mg) were added to an acetonitrile (0.4 mL) solution of benzyl bromide (0.050 mmol). The resulting reaction mixture was stirred at 45 °C for 5 hours. The mixture solution was cooled to room temperature, and the resin was then removed by filtration to concentrate the filtrate. The resulting residue was dissolved in acetonitrile (1.0 mL), and phenyl isocyanate (0.008 mL, 0.05 mmol) was then added to the obtained solution. The mixture solution was stirred at room temperature for 1 hour, loaded onto a Varian™ SCX column and washed with methanol (15 mL). The obtained crude product was eluted with a solution of 2 M NH₃ in methanol (6 mL) and concentrated to thereby provide (S)-1-benzyl-3-[N-[3-(trifluoromethyl)benzoyl]glycyl]aminopyrrolidine (Compd. No. 239) (9.0 mg, 44%). The purity was determined by RPLC/MS (99%). ESI/MS m/e 406.0 (M⁺+H, C₂₁H₂₂F₃N₃O₂).

[Example 575] Synthesis of (R)-1-(4-butylbenzyl)-3-[[N-(3-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (Compd. No. 1648)

[0159] Acetic acid (0.060 mL) was added to a mixture of (R)-3-[N-[3-(trifluoromethyl)benzoyl]glycyl]aminopyrrolidine (0.050 mL) with 4-butylbenzaldehyde (0.18 mmol), NaBH₃CN (0.23 mmol) and methanol (1.85 mL). The resulting reaction mixture was stirred at 60 °C for 12 hours, cooled to room temperature, loaded onto a Varian™ SCX column and washed with methanol (15 mL). The obtained crude product was eluted with a solution of 2 M NH₃ in methanol (5 mL) and concentrated to thereby afford (R)-1-(4-butylbenzyl)-3-[[N-(3-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (Compd. No. 1648) (20.6 mg, 89%). The purity was determined by RPLC/MS (91%). ESI/MS m/e 462.2 (M⁺+H, C₂₅H₃₀F₃N₃O₂).

[Examples 576 to 738]

[0160] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 574 or 575. The obtained crude products, if necessary,

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were purified by preparative TLC or chromatography (HPLC-C₁₈) to provide the objective compounds. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 8.

Table 8

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
576	240	C ₂₁ H ₂₁ F ₄ N ₃ O ₂	424.0	10.2	48
577	241	C ₂₁ H ₂₁ ClF ₃ N ₃ O ₂	440.0	12.1	55
578	242	C ₂₁ H ₂₀ Cl ₂ F ₃ N ₃ O ₂	474.0	13.9	59
579	243	C ₂₁ H ₂₀ Cl ₂ F ₃ N ₃ O ₂	474.0	13.8	58
580	244	C ₂₂ H ₂₄ F ₃ N ₃ O ₂	420.0	13.1	62
581	245	C ₂₁ H ₂₁ F ₄ N ₃ O ₂	424.0	11.9	56
582	246	C ₂₁ H ₂₁ ClF ₃ N ₃ O ₂	440.0	8.5	39
583	247	C ₂₁ H ₂₀ Cl ₂ F ₃ N ₃ O ₂	474.0	10.5	44
584	248	C ₂₂ H ₂₄ CF ₃ N ₃ O ₃	436.0	11.0	51
585	249	C ₂₂ H ₂₁ ClF ₆ N ₃ O ₂	474.0	12.8	54
586	250	C ₂₂ H ₂₄ F ₃ N ₃ O ₂	420.0	11.0	52
587	251	C ₂₁ H ₂₁ F ₄ N ₃ O ₂	424.0	13.5	64
588	252	C ₂₂ H ₂₄ F ₃ N ₃ O ₃	436.0	11.8	54
589	253	C ₂₂ H ₂₄ F ₃ N ₃ O ₂	420.0	11.1	53
590	254	C ₂₁ H ₂₀ ClF ₃ N ₄ O ₄	485.0	2.4	10
591	255	C ₂₁ H ₂₁ F ₃ N ₄ O ₄	451.0	12.2	54
592	256	C ₂₁ H ₂₁ F ₃ N ₄ O ₄	451.0	11.4	51
593	257	C ₂₂ H ₂₁ F ₆ N ₃ O ₂	474.0	11.1	47
594	258	C ₂₄ H ₂₆ F ₃ N ₃ O ₄	478.0	15.3	64
595	259	C ₂₂ H ₂₃ ClF ₃ N ₃ O ₂	420.0	6.4	31
596	260	C ₂₁ H ₂₀ Cl ₂ F ₃ N ₃ O ₂	474.0	12.1	51
597	261	C ₂₂ H ₂₁ ClF ₆ N ₃ O ₂	474.0	13.6	57
598	262	C ₂₁ H ₂₁ BrF ₃ N ₃ O ₂	484.0	15.2	63
599	263	C ₂₁ H ₂₁ BrF ₃ N ₃ O ₂	484.0	14.5	60
600	264	C ₂₇ H ₂₆ F ₃ N ₃ O ₃	498.0	9.3	37
601	265	C ₂₁ H ₂₁ BrF ₃ N ₃ O ₂	484.0	11.6	48
602	266	C ₂₂ H ₂₂ F ₃ N ₃ O ₄	450.0	8.9	40
603	267	C ₂₂ H ₂₄ F ₃ N ₃ O ₃	436.0	10.3	47
604	268	C ₂₃ H ₂₅ F ₃ N ₄ O ₃	463.0	6.3	27
605	269	C ₂₂ H ₂₄ F ₃ N ₃ O ₄ S	484.0	8.0	33
606	270	C ₂₃ H ₂₄ F ₃ N ₃ O ₄	464.0	8.9	38
607	271	C ₂₁ H ₂₀ F ₅ N ₃ O ₂	442.0	6.1	28
608	272	C ₂₁ H ₂₂ F ₃ N ₃ O ₃	422.0	13.6	59
609	273	C ₂₂ H ₂₁ F ₃ N ₄ O ₂	431.0	12.6	59
610	274	C ₂₂ H ₂₁ F ₃ N ₄ O ₂	431.0	7.7	36
611	275	C ₂₂ H ₂₁ F ₃ N ₄ O ₂	431.0	12.7	59

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Table 8 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	612	C ₂₁ H ₂₀ F ₅ N ₃ O ₂	442.0	11.7	53
	613	C ₂₇ H ₂₆ F ₃ N ₃ O ₂	482.0	9.5	39
	614	C ₂₃ H ₂₄ F ₃ N ₃ O ₄	464.0	13.0	56
10	615	C ₂₂ H ₂₁ F ₆ N ₃ O ₃	490.0	10.4	42
	616	C ₂₂ H ₂₁ F ₆ N ₃ O ₃	490.0	12.0	49
	617	C ₂₂ H ₂₂ F ₃ N ₃ O ₄	450.0	4.9	22
15	618	C ₂₅ H ₃₀ F ₃ N ₃ O ₂	462.0	12.0	52
	619	C ₂₀ H ₂₃ F ₃ N ₄ O ₃	425.0	8.1	38
	620	C ₂₇ H ₂₅ ClF ₃ N ₃ O ₂	516.0	4.8	19
20	621	C ₂₁ H ₂₂ F ₃ N ₃ O ₂	406.0	4.8	24
	622	C ₂₁ H ₂₁ F ₄ N ₃ O ₂	424.0	4.5	21
	623	C ₂₁ H ₂₁ ClF ₃ N ₃ O ₂	440.0	5.8	26
25	624	C ₂₁ H ₂₀ Cl ₂ F ₃ N ₃ O ₂	474.0	8.1	34
	625	C ₂₁ H ₂₀ Cl ₂ F ₃ N ₃ O ₂	474.0	8.0	34
	626	C ₂₂ H ₂₄ F ₃ N ₃ O ₂	420.0	6.0	29
30	627	C ₂₁ H ₂₁ F ₄ N ₃ O ₂	424.0	6.2	29
	628	C ₂₁ H ₂₁ ClF ₃ N ₃ O ₂	440.0	4.5	20
	629	C ₂₁ H ₂₀ Cl ₂ F ₃ N ₃ O ₂	474.0	5.1	22
35	630	C ₂₂ H ₂₄ CF ₃ N ₃ O ₃	436.0	4.2	19
	631	C ₂₂ H ₂₁ ClF ₆ N ₃ O ₂	474.0	6.0	25
	632	C ₂₂ H ₂₄ F ₃ N ₃ O ₂	420.0	4.3	21
40	633	C ₂₁ H ₂₁ F ₄ N ₃ O ₂	424.0	8.2	39
	634	C ₂₂ H ₂₄ F ₃ N ₃ O ₃	436.0	12.2	56
	635	C ₂₂ H ₂₄ F ₃ N ₃ O ₂	420.0	8.1	39
45	636	C ₂₁ H ₂₀ ClF ₃ N ₄ O ₄	485.0	13.7	57
	637	C ₂₁ H ₂₁ F ₃ N ₄ O ₄	451.0	15.1	67
	638	C ₂₁ H ₂₁ F ₃ N ₄ O ₄	451.0	16.6	74
50	639	C ₂₂ H ₂₁ F ₆ N ₃ O ₂	474.0	12.6	53
	640	C ₂₄ H ₂₆ F ₃ N ₃ O ₄	478.0	14.5	61
	641	C ₂₂ H ₂₃ ClF ₃ N ₃ O ₂	420.0	8.4	37
55	642	C ₂₁ H ₂₀ Cl ₂ F ₃ N ₃ O ₂	474.0	13.5	57
	643	C ₂₂ H ₂₁ ClF ₆ N ₃ O ₂	474.0	3.7	16
	644	C ₂₁ H ₂₁ BrF ₃ N ₃ O ₂	484.0	7.2	30
	645	C ₂₁ H ₂₁ BrF ₃ N ₃ O ₂	484.0	6.7	28
	646	C ₂₇ H ₂₆ F ₃ N ₃ O ₃	498.0	4.2	17
	647	C ₂₁ H ₂₁ BrF ₃ N ₃ O ₂	484.0	6.3	26
	648	C ₂₂ H ₂₂ F ₃ N ₃ O ₄	450.0	2.4	11
	649	C ₂₂ H ₂₄ F ₃ N ₃ O ₃	436.0	1.9	9

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Table 8 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	650	C ₂₃ H ₂₅ F ₃ N ₄ O ₃	463.0	5.0	22
	651	C ₂₂ H ₂₄ F ₃ N ₃ O ₄ S	484.0	2.5	10
	652	C ₂₃ H ₂₄ F ₃ N ₃ O ₄	464.0	3.3	14
10	653	C ₂₁ H ₂₀ F ₅ N ₃ O ₂	442.0	4.5	20
	654	C ₂₁ H ₂₂ F ₃ N ₃ O ₃	422.0	7.9	34
	655	C ₂₂ H ₂₁ F ₃ N ₄ O ₂	431.0	6.5	30
15	656	C ₂₂ H ₂₁ F ₃ N ₄ O ₂	431.0	14.2	66
	657	C ₂₂ H ₂₁ F ₃ N ₄ O ₂	431.0	14.9	69
	658	C ₂₁ H ₂₀ F ₅ N ₃ O ₂	442.0	13.6	62
20	659	C ₂₇ H ₂₆ F ₃ N ₃ O ₂	482.0	3.9	16
	660	C ₂₃ H ₂₄ F ₃ N ₃ O ₄	464.0	15.2	66
	661	C ₂₂ H ₂₁ F ₆ N ₃ O ₃	490.0	16.1	66
25	662	C ₂₂ H ₂₁ F ₆ N ₃ O ₃	490.0	13.6	56
	663	C ₂₂ H ₂₂ F ₃ N ₃ O ₄	450.0	5.4	24
	664	C ₂₅ H ₃₀ F ₃ N ₃ O ₂	462.0	10.9	47
30	665	C ₂₀ H ₂₃ F ₃ N ₄ O ₃	425.0	12.0	57
	666	C ₂₇ H ₂₅ ClF ₃ N ₃ O ₂	516.0	1.5	6
	667	C ₂₈ H ₂₇ F ₃ N ₄ O ₃	525	21.5	62
35	668	C ₂₂ H ₂₄ F ₃ N ₃ O ₂ S	452	16.9	57
	669	C ₂₃ H ₂₆ F ₃ N ₃ O ₄	466	20.5	67
	670	C ₂₂ H ₂₃ F ₃ N ₄ O ₄	465	16.8	55
40	671	C ₂₈ H ₃₆ F ₃ N ₃ O ₂	504	21.0	63
	672	C ₂₅ H ₂₃ BrF ₃ N ₃ O ₂	534	26.6	75
	673	C ₁₉ H ₁₉ F ₃ N ₄ O ₅	441	21.3	73
45	674	C ₂₃ H ₂₆ F ₃ N ₃ O ₄	467	33.6	84
	675	C ₂₄ H ₂₈ F ₃ N ₃ O ₅	496	34.8	82
	676	C ₂₂ H ₂₁ F ₃ N ₄ O ₆	495	32.6	77
50	677	C ₂₃ H ₂₄ F ₃ N ₃ O ₅	480	36.6	89
	678	C ₂₂ H ₂₁ BrF ₃ N ₃ O ₄	529	30.8	69
	679	C ₂₄ H ₂₆ F ₃ N ₃ O ₂	446	32.7	86
55	680	C ₂₂ H ₂₄ F ₃ N ₃ O ₂	420	18.6	51
	681	C ₂₁ H ₂₀ F ₃ N ₅ O ₆	496	20.5	49
	682	C ₂₅ H ₂₄ F ₃ N ₃ O ₂	456	22.5	58
	683	C ₂₅ H ₂₄ F ₃ N ₃ O ₂	456	21.6	55
	684	C ₃₅ H ₃₄ F ₃ N ₃ O ₄	618	27.3	53
	685	C ₂₃ H ₂₆ F ₃ N ₃ O ₄	466	25.5	64
	686	C ₂₃ H ₂₅ F ₃ N ₄ O ₆	511	38.0	88
	687	C ₂₈ H ₂₈ F ₃ N ₃ O ₃	512	38.3	89

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Table 8 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	688	C ₂₃ H ₂₅ F ₃ N ₄ O ₃	463	27.1	62
	689	C ₂₇ H ₂₆ F ₃ N ₃ O ₂	482	22.4	57
	690	C ₂₂ H ₂₄ F ₃ N ₃ O ₄	452	13.5	58
10	691	C ₂₄ H ₂₈ F ₃ N ₃ O ₃	464	16.7	70
	692	C ₂₂ H ₂₃ F ₄ N ₃ O ₃	454	15.8	68
	693	C ₂₃ H ₂₆ F ₃ N ₃ O ₃	450	15.7	68
15	694	C ₂₃ H ₂₄ F ₃ N ₃ O ₄	464	16.3	68
	695	C ₂₂ H ₂₃ BrF ₃ N ₃ O ₃	513	15.0	57
	696	C ₁₇ H ₁₇ ClF ₃ N ₅ O ₂ S	448	6.9*	23
20	697	C ₂₀ H ₂₂ F ₃ N ₅ O ₃ S	470	1.7*	6
	698	C ₂₂ H ₂₂ F ₃ N ₅ O ₂	446	2.3*	8
	699	C ₂₆ H ₃₃ F ₃ N ₄ O ₃	507	25.3*	51
25	700	C ₂₁ H ₂₀ F ₃ N ₅ O ₆	496	4.0*	8
	701	C ₂₂ H ₂₄ F ₃ N ₃ O ₄	452	3.6*	13
	702	C ₂₃ H ₂₅ BrF ₃ N ₃ O ₄	544	28.4	Q
30	703	C ₂₄ H ₂₈ F ₃ N ₃ O ₅	496	1.4	6
	704	C ₂₃ H ₂₆ F ₃ N ₃ O ₄	466	7.3	33
	705	C ₂₄ H ₂₈ F ₃ N ₃ O ₅	496	12.6	53
35	706	C ₂₄ H ₂₈ F ₃ N ₃ O ₃	464	24.5	Q
	707	C ₂₃ H ₂₅ BrF ₃ N ₃ O ₄	544	22.2	Q
	708	C ₂₉ H ₃₀ F ₃ N ₃ O ₄	542	28.6	Q
40	709	C ₂₆ H ₂₆ F ₃ N ₃ O ₃	486	35.4	Q
	710	C ₂₄ H ₂₈ F ₃ N ₃ O ₄	480	8.1	35
	711	C ₂₃ H ₂₆ F ₃ N ₃ O ₅	482	27.9	Q
45	712	C ₂₃ H ₂₄ F ₃ N ₃ O ₃	448	5.9	28
	713	C ₂₃ H ₂₅ F ₃ IN ₃ O ₄	592	24.0	85
	714	C ₂₂ H ₂₄ F ₃ N ₃ O ₄	452	3.4	16
50	715	C ₂₂ H ₂₂ F ₃ N ₃ O ₄	450	3.4	16
	716	C ₂₁ H ₂₁ F ₃ IN ₃ O ₂	532	18.1	72
	717	C ₂₁ H ₂₁ BrF ₃ N ₃ O ₂	484	17.4	76
55	718	C ₁₉ H ₁₉ F ₃ N ₄ O ₄ S	457	16.8	77
	719	C ₂₀ H ₂₂ F ₃ N ₃ O ₃	410	13.6	70
	720	C ₂₂ H ₂₀ ClF ₆ N ₃ O ₂	508	18.6	77
	721	C ₂₁ H ₂₀ ClF ₃ N ₄ O ₄	485	17.0	74
	722	C ₂₁ H ₂₀ ClF ₄ N ₃ O ₂	458	17.0	78
	723	C ₂₁ H ₂₀ ClF ₄ N ₃ O ₂	458	17.6	81

Notes: * indicates "yield (mg) of trifluoroacetate".

Q means "Quantitative".

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Table 8 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
724	1320	C ₂₁ H ₂₀ BrF ₄ N ₃ O ₂	502	18.5	77
725	1390	C ₂₆ H ₃₂ F ₃ N ₃ O ₂	476	16.1	51
726	1391	C ₂₃ H ₂₆ F ₃ N ₃ O ₂	434	20.0	76
727	1392	C ₂₂ H ₂₃ ClF ₃ N ₃ O ₂	454	20.0	67
728	1393	C ₂₃ H ₂₆ F ₃ N ₃ O ₂	434	20.1	70
729	1394	C ₂₂ H ₂₃ F ₃ N ₄ O ₄	465	18.4	60
730	1395	C ₂₃ H ₂₄ F ₃ N ₃ O ₂	432	21.4	75
731	1396	C ₂₆ H ₂₆ F ₃ N ₃ O ₂	470	20.4	66
732	1397	C ₂₁ H ₂₀ Br ₂ F ₃ N ₃ O ₂	562	14.5	54
733	1398	C ₂₂ H ₂₂ Cl ₂ F ₃ N ₃ O ₂	488	10.8	47
734	1399	C ₂₂ H ₂₂ Cl ₂ F ₃ N ₃ O ₂	488	9.4	40
735	1400	C ₂₂ H ₂₃ ClF ₃ N ₃ O ₂	454	19.1	88
736	1614	C ₂₂ H ₂₁ F ₆ N ₃ S	506.0	24.2	96
737	2050	C ₂₀ H ₂₂ F ₃ N ₃ O ₂ S	426	6.0	30
738	2051	C ₂₁ H ₂₃ F ₃ N ₄ O ₂	421	6.5	32

[Examples 739 to 748]

[0161] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 575. The obtained products, if necessary, were purified with preparative TLC to afford the objective compounds. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 9.

Table 9

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
739	1650	C ₂₄ H ₂₈ F ₃ N ₃ O ₂	448.0	20.4	91
740	1706	C ₂₃ H ₂₅ F ₃ N ₄ O ₃	463.2	3.7	11
741	1707	C ₂₂ H ₂₅ F ₃ N ₄ O ₂ S	467.0	10.3	29
742	1708	C ₂₃ H ₂₇ F ₃ N ₄ O ₂	449.2	11.4	34
743	1709	C ₂₄ H ₂₉ F ₃ N ₄ O ₂	463.2	15.2	44
744	1775	C ₂₂ H ₂₅ F ₃ N ₄ O ₄	467.2	9.2	26.3
745	1776	C ₂₂ H ₂₅ F ₃ N ₄ O ₄	467.2	8.9	25.4
746	1787	C ₂₄ H ₂₉ F ₃ N ₄ O ₂	463.2	5.6	16.1
747	1802	C ₂₃ H ₂₇ F ₃ N ₄ O ₄	481.2	11.7	32.5
748	1803	C ₂₂ H ₂₅ F ₃ N ₄ O ₃	451.2	9.6	28.4

[Example 749] Synthesis of (R)-3-[[N-2-amino-5-trifluoromethoxybenzoyl]glycyl]amino]-1-(3-hydroxy-4-methoxybenzyl)pyrrolidine (Compd. No. 1896)

[0162] Acetic acid (0.050 mL) was added to a mixture of (R)-3-[N-[2-(tert-butoxycarbonylamino)-5-(trifluoromethoxybenzoyl]glycyl]amino]pyrrolidine (0.050 mmol) with 3-hydroxy-4-methoxybenzaldehyde (0.060 mmol), NaBH₃CN (0.15 mmol) and methanol (1.3 mL). The resulting reaction mixture was stirred at 60 °C for 8 hours, cooled to room temperature, then loaded onto a Varian™ SCX column and washed with methanol (10 mL). The obtained crude product was

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eluted with a solution of 2 M NH₃ in methanol (5 mL) and concentrated. A 1,4-dioxane solution of 4 M HCl was added to the prepared residue, and the solution was stirred at room temperature overnight, concentrated and then purified by preparative TLC to thereby provide (R)-3-[[N-(2-amino-5-trifluoromethoxybenzoyl)glycyl]amino]-1-(3-hydroxy-4-methoxybenzyl)pyrrolidine (Compd. No. 1896) (9.1 mg, 38%). The purity was determined by RPLC/MS (93%). ESI/MS m/e 483 (M⁺+H, C₂₂H₂₅F₃N₄O₅).

[Examples 750 to 757]

[0163] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 749. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 10.

Table 10

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
750	1897	C ₂₂ H ₂₅ F ₃ N ₄ O ₃ S	483	22.7	94.1
751	1898	C ₂₃ H ₂₇ F ₃ N ₄ O ₃	465	12.2	52.5
752	1899	C ₂₄ H ₂₉ F ₃ N ₄ O ₃	479	14.4	60.2
753	1900	C ₂₂ H ₂₅ F ₃ N ₄ O ₅	483	2.6	10.8
754	1901	C ₂₄ H ₂₉ F ₃ N ₄ O ₃	479	14.5	60.6
755	1902	C ₂₃ H ₂₅ F ₃ N ₄ O ₄	479	12.0	50.2
756	1915	C ₂₃ H ₂₇ F ₃ N ₄ O ₅	467.2	2.5	6.7
757	1916	C ₂₂ H ₂₅ F ₃ N ₄ O ₄	467.2	3.1	8.9

[Example 758] Synthesis of (R)-3-[[N-(2-amino-5-trifluoromethyl)benzoyl]glycyl]amino]-1-(4-vinylbenzyl)pyrrolidine (Compd. No. 1701)

[0164] A mixture of (R)-3-[[N-(2-amino-5-(trifluoromethyl)benzoyl)glycyl]amino]pyrrolidine (0.050 mmol) with 4-vinylbenzyl chloride (9.9 mg, 0.065 mL), a piperidinopolystyrene (60 mg), acetonitrile (1.0 mL) and chloroform (0.30 mL) was stirred at 50 °C for 12 hours. The resulting reaction mixture was cooled to room temperature, loaded onto a Varian™ SCX column and washed with methanol (15 mL). The obtained crude product was eluted with solution of 2 M NH₃ in a methanol (5 mL) and concentrated to thereby afford (R)-3-[[N-(2-amino-5-(trifluoromethyl)benzoyl)glycyl]amino]-1-(4-vinylbenzyl)pyrrolidine (Compd. No. 1701) (19.6 mg, 88%). The purity was determined by RPLC/MS (92%). ESI/MS m/e 547.2 (M⁺+H, C₂₃H₂₅ClF₃N₄O₂).

[Examples 759 to 762]

[0165] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 758. The obtained products, if necessary, were purified with preparative TLC to provide the objective substances. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 11.

Table 11

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
759	1702	C ₂₂ H ₂₅ F ₃ N ₄ O ₃	451.2	5.3	24
760	1703	C ₂₂ H ₂₃ F ₃ N ₄ O ₄	465.2	5.0	22
761	1704	C ₂₁ H ₂₃ F ₃ N ₄ O ₃	437.2	20.9	96
762	1705	C ₂₁ H ₂₁ Cl ₂ F ₃ N ₄ O ₂	489.2	9.3	38

[Example 763] Synthesis of (R)-3-[[N-(2-amino-5-(trifluoromethoxy)benzoyl)glycyl]amino]-1-(2,4-dichlorobenzyl)pyrrolidine (Compd. No. 1905)

[0166] A mixture of (R)-3-[[N-(2-amino-5-(trifluoromethoxy)benzoyl)glycyl]amino]pyrrolidine (0.050 mmol) with 2,4-dichlorobenzyl chloride (0.066 mL), a piperidinomethylpolystyrene (60 mg), acetonitrile (0.8 mL) and chloroform (0.5 mL) was stirred at 60 °C for 12 hours. The resulting reaction mixture was cooled to room temperature, loaded onto a Varian™ SCX column and washed with a 50% chloroform/methanol (10 mL) and methanol (10 mL). The obtained crude product was eluted with a solution of 2 M NH₃ in methanol (5 mL) and concentrated. A 1,4-dioxane (2 mL) solution of 4 M HCl was added to the resulting residue, and the obtained mixture was stirred at room temperature overnight, concentrated and then purified by preparative TLC to afford (R)-3-[[N-(2-amino-5-(trifluoromethoxy)benzoyl)glycyl]amino]-1-(2,4-dichlorobenzyl)pyrrolidine (Compd. No. 1905) (17.6 mg, 70%). The purity was determined by RPLC/MS (93%). ESI/MS m/e 505 (M⁺+H, C₂₁H₂₁Cl₂F₃N₄O₃).

[Examples 764 to 770]

[0167] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 763. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 12.

Table 12

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
764	1906	C ₂₂ H ₂₃ F ₃ N ₄ O ₅	481	9.4	39.1
765	1907	C ₂₁ H ₂₃ F ₃ N ₄ O ₄	453	7.5	33.2
766	1908	C ₂₂ H ₂₅ F ₃ N ₄ O ₄	467	7.7	33.0
767	2180	C ₂₂ H ₂₄ ClF ₃ N ₄ O ₂	469	1.3	26
768	2181	C ₂₃ H ₂₅ F ₃ N ₆ O ₃	491	4.3	52
769	2182	C ₁₉ H ₂₂ F ₃ N ₅ O ₂ S	442	7.0	51
770	1909	C ₂₃ H ₂₅ F ₃ N ₄ O ₃	463	8.7	37.6

[Example 771] Synthesis of (R)-3-[[N-(2-amino-5-trifluoromethoxybenzoyl)glycyl]amino]-1-(2-amino-4-chlorobenzyl)pyrrolidine (Compd. No. 1921)

[0168] A mixture of (R)-3-[[N-(2-amino-5-trifluoromethoxybenzoyl)glycyl]amino]pyrrolidine (0.050 mmol) with 4-chloro-2-nitrobenzyl chloride (0.050 mmol), a piperidinomethylpolystyrene (60 mg), acetonitrile (1.0 mL) and chloroform (0.7 mL) was stirred at 50 °C overnight. The resulting reaction mixture was cooled, loaded onto a Varian™ SCX column and washed with 50% chloroform/methanol (10 mL) and methanol (10 mL). The obtained crude product was eluted with a solution of 2 M NH₃ in methanol (5 mL) and concentrated. Ethanol (3 mL) and 10% palladium carbon were added to the resulting residue, and the solution was stirred at room temperature under a hydrogen atmosphere for 1.5 hours. The obtained solution was filtered, concentrated and then purified by preparative TLC to thereby provide (R)-3-[[N-(2-amino-5-trifluoromethoxybenzoyl)glycyl]amino]-1-(2-amino-4-chlorobenzyl)pyrrolidine (Compd. No. 1921) (2.2 mg, 6%). The purity was determined by RPLC/MS (81%). ESI/MS m/e 486.2 (M⁺+H, C₂₁H₂₃ClF₃N₅O₃).

[Example 772] Synthesis of (R)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-(4-bromo-2-fluorobenzyl)pyrrolidine (Compd. No. 2120)

[0169] A methanol (0.50 mL) solution of NaBH₃CN (0.25 mmol) was added to a mixture of (R)-3-[[N-(2-tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (0.050 mmol) with 4-bromo-2-fluorobenzaldehyde (0.015 mmol), methanol (1.5 mL) and acetic acid (0.016 mL). The resulting reaction mixture was stirred at 50 °C overnight, cooled to room temperature, then loaded onto a Varian™ SCX column and washed with methanol (5 mL×2). The obtained product was eluted with a solution of 2 M NH₃ in methanol (5 mL) and concentrated. The resulting residue was dissolved in methanol (0.25 mL), and a dioxane solution of 4 M HCl was added to the obtained solution. The resulting solution was stirred at room temperature for 5 hours and concentrated. The obtained residue was dissolved in methanol, loaded onto a Varian™ SCX column and washed with methanol (5 mL×2). The resulting crude product was eluted with a solution of 2 M NH₃ in methanol (5 mL) and concentrated. The obtained residue was dissolved in

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ethyl acetate (0.5 mL), loaded onto a Varian™ SCX column, eluted with ethyl acetate/methanol = 5:1 (6 mL) and concentrated to thereby afford (R)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-(4-bromo-2-fluorobenzyl)pyrrolidine (Compd. No. 2120) (16.0 mg, 31%). The purity was determined by RPLC/MS (99%). ESI/MS m/e 517.0 (M⁺+H, C₂₁H₂₁BrF₄N₄O₂).

[Examples 773 to 793]

[0170] The compounds used in the present invention were synthesized by using the respective starting materials and reactants according to the method of Example 772. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 13.

Table 13

Example	Compd. No.	Molecular Formula	EMI/MS me	Yield (mg)	Yield (%)
773	2083	C ₂₂ H ₂₄ BrF ₃ N ₄ O ₄	545.2	2.9	11
774	2084	C ₂₃ H ₂₇ F ₃ N ₄ O ₅	497.2	5.1	21
775	2085	C ₂₂ H ₂₅ F ₃ N ₄ O ₄	467.2	3.1	13
776	2086	C ₂₁ H ₂₂ ClF ₃ N ₄ O ₃	471.0	4.6	20
777	2087	C ₂₃ H ₂₈ F ₃ N ₅ O ₂	464.2	5.6	24
778	2088	C ₂₅ H ₃₂ F ₃ N ₅ O ₂	492.2	5.9	24
779	2089	C ₂₁ H ₂₁ F ₅ N ₄ O ₂	457.2	4.5	20
780	2090	C ₂₇ H ₂₇ F ₃ N ₄ O ₃	513.2	8.0	31
781	2118	C ₂₁ H ₂₃ F ₃ N ₄ O ₄	453.1	2.7	12
782	2119	C ₂₁ H ₂₃ F ₃ N ₄ O ₄	453.1	4.3	19
783	2121	C ₂₂ H ₂₅ F ₃ N ₄ O ₄	467.0	1.2	2
784	2122	C ₂₁ H ₂₁ ClF ₄ N ₄ O ₂	472.9	13.1	28
785	2123	C ₂₂ H ₂₂ F ₃ N ₅ O ₆	510.1	13.1	51
786	2124	C ₂₁ H ₂₁ ClF ₃ N ₅ O ₄	500.1	15.6	62
787	2125	C ₂₂ H ₂₄ F ₃ N ₅ O ₅	496.0	16.0	65
788	2126	C ₂₂ H ₂₄ F ₃ N ₅ O ₄	480.1	15.6	65
789	2137	C ₂₂ H ₂₄ ClF ₃ N ₄ O ₂	469.2	2.6	11
790	2138	C ₂₆ H ₂₉ F ₃ N ₆ O ₂	515.3	25.1	98
791	2139	C ₂₀ H ₂₄ ClF ₃ N ₆ O ₂	473.2	25.0	98
792	2149	C ₂₁ H ₂₂ F ₃ N ₅ O ₅	482.3	4.9	34
793	2157	C ₂₂ H ₂₅ F ₃ N ₄ O ₃	451.2	15.5	70

[Example 794] Synthesis of (R)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-(2,4-dimethoxypyrimidin-5-ylmethyl)pyrrolidine (Compd. No. 2175)

[0171] (R)-3-[[N-(2-Amino-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (17.2 mg, 0.04 mmol) was dissolved in THF (1 mL), and 2,4-dimethoxy-5-pyrimidinecarboxaldehyde (6.7 mg, 0.04 mmol) was added to the resulting solution. Sodium triacetoxyborohydride (12.7 mg, 0.06 mmol) and glacial acetic acid (2.4 mg, 0.04 mmol) were subsequently added to the mixture. The resulting mixture was stirred at 50 °C for 24 hours and then concentrated. The residue was dissolved in dichloromethane (1 mL) and washed with a 1 M aqueous solution (1 mL) of NaOH. The organic layer was collected and concentrated, and a dichloromethane solution of 25% trifluoroacetic acid (1 mL) was added. The resulting mixture was stirred at room temperature for 1 hour and then concentrated. The obtained residue was purified by HPLC to thereby provide (R)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-(2,4-dimethoxypyrimidin-5-ylmethyl)pyrrolidine (Compd. No. 2175) (18.6 mg, 78%). The purity was determined by RPLC/MS (98%). ESI/MS m/e 483 (M⁺+H, C₂₁H₂₅F₃N₆O₄).

[Examples 795 to 803]

[0172] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according the method of Example 794. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 14.

Table 14

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
795	2165	C ₁₈ H ₂₁ F ₃ N ₆ O ₂	411	2.0	27
796	2166	C ₁₈ H ₂₀ F ₃ N ₅ O ₂ S	428	9.9	66
797	2167	C ₂₄ H ₂₅ F ₃ N ₆ O ₂	487	15.1	73
798	2169	C ₂₄ H ₂₉ F ₃ N ₄ O ₂	463	1.2	24
799	2170	C ₂₆ H ₂₅ ClF ₃ N ₅ O ₂	520	6.0	40
800	2171	C ₁₉ H ₂₃ F ₃ N ₆ O ₂	425	16.8	88
801	2174	C ₂₃ H ₂₄ BrF ₃ N ₄ O ₂ S ₂	591	5.3	53
802	2178	C ₂₅ H ₂₈ F ₃ N ₅ O ₄	518	5.4	62
803	2179	C ₂₅ H ₂₈ F ₃ N ₅ O ₃	502	6.3	60

[Example 804] Synthesis of (R)-1-(2-amino-4,5-methylenedioxybenzyl)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (Compd. No. 2127)

[0173] A mixture of (R)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-(4,5-methylenedioxy-2-nitrobenzyl)pyrrolidine (30.5 mg) with 10% Pd carbon (6 mg) and methanol (3 mL) was stirred at room temperature under a hydrogen atmosphere for 10 hours. The palladium catalyst was filtered through Celite, and the filtrate was concentrated and purified by solid-phase extraction (Bond Elut™ SI, 20% methanol/ethyl acetate) to thereby afford (R)-1-(2-amino-4,5-methylenedioxybenzyl)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (Compd. No. 2127) (21.9 mg, 76%). The purity was determined by RPLC/MS (95%). ESI/MS m/e 480.1 (M⁺+H, C₂₂H₂₄F₃N₅O₄).

[Examples 805 to 806]

[0174] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 804. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 15.

Table 15

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
805	2128	C ₂₂ H ₂₆ F ₃ N ₅ O ₃	466.0	8.6	30
806	2129	C ₂₂ H ₂₆ F ₃ N ₅ O ₂	450.1	13.1	37

[Example 807] Synthesis of (R)-1-(3-amino-4-chlorobenzyl)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (Compd. No. 2132)

[0175] A mixture of (R)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-(4-chloro-3-nitrobenzyl)pyrrolidine (32.6 mg) with 10% palladium carbon (8 mg), ethyl acetate (2.7 mL) and methanol (0.3 mL) was stirred at room temperature under a hydrogen atmosphere for 15 hours. The palladium carbon was removed by filtration, and the filtrate was concentrated and purified by solid-phase extraction (Bond Elut™ SI, 20% methanol/ethyl acetate) to thereby provide (R)-1-(3-amino-4-chlorobenzyl)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (Compd. No. 2132) (10.5 mg, 34%). The purity was determined by RPLC/MS (84%). ESI/MS m/e 470.2 (M⁺+H, C₂₁H₂₃F₃N₅O₂).

[Example 808] Synthesis of (R)-1-(2-amino-4,5-methylenedioxybenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine

[0176] A methanol (1.50 mL) solution of NaBH₃CN (0.75 mmol) was added to a mixture of (R)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (0.150 mmol) with 4,5-methylenedioxy-2-nitrobenzaldehyde (0.45 mmol), methanol (4.5 mL) and acetic acid (0.048 mL). The resulting reaction mixture was stirred at 50 °C overnight, cooled to room temperature, loaded onto a Varian™ SCX column and washed with methanol. The obtained crude product was eluted with a 2 M methanol solution of NH₃ and concentrated to thereby afford (R)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]-1-(4,5-methylenedioxy-2-nitrobenzyl)pyrrolidine.

[0177] A mixture of the resulting (R)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]-1-(4,5-methylenedioxy-2-nitrobenzyl)pyrrolidine (0.150 mmol) with 10% Pd carbon (22 mg) and methanol (4.5 mL) was stirred at room temperature under a hydrogen atmosphere overnight. The palladium catalyst was removed by filtration, and the filtrate was concentrated to thereby afford (R)-1-(2-amino-4,5-methylenedioxybenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (87.1 mg, quantitative). Any noticeable by-product was not detected in TLC.

[0178] Further, (R)-1-(3-amino-4-methoxybenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine and (R)-1-(3-amino-4-methylbenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 808.

[0179] (R)-1-(3-amino-4-methoxybenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine: 101 mg, quantitative. Any noticeable by-product was not detected in TLC.

[0180] (R)-1-(3-amino-4-methylbenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine: 97.2 mg, quantitative. Any noticeable by-product was not detected in TLC.

[Example 809] Synthesis of (R)-1-(3-amino-4-chlorobenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine

[0181] A methanol (1.50 mL) solution of NaBH₃CN (0.75 mmol) was added to a mixture of (R)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (0.150 mmol) with 4-chloro-3-nitrobenzaldehyde (0.45 mmol), methanol (4.5 mL) and acetic acid (0.048 mL). The resulting reaction mixture was then stirred at 50 °C overnight, cooled to room temperature, loaded onto a Varian™ SCX column and washed with methanol. The obtained product was eluted with a 2 M methanol solution of NH₃ and concentrated to thereby provide (R)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]-1-(4-chloro-3-nitrobenzyl)pyrrolidine.

[0182] A mixture of the resulting (R)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]-1-(4-chloro-3-nitrobenzyl)pyrrolidine with 10% Pd carbon (22 mg), ethyl acetate (2.7 mL) and methanol (0.3 mL) was stirred at room temperature under a hydrogen atmosphere for 15 hours. The palladium catalyst was removed by filtration, and the filtrate was concentrated to afford (R)-1-(3-amino-4-chlorobenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (89.7 mg, quantitative). Any noticeable by-product was not detected in TLC.

[Example 810] Synthesis of (R)-1-(3-amino-4-hydroxybenzyl)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (Compd. No. 2187)

[0183] A 4 M HCl dioxane (2.0 mL) solution of (R)-1-(3-amino-4-hydroxybenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (20 mg) synthesized according to the method of Example 808 was stirred at room temperature overnight. The solution was concentrated, and the residue was then dissolved in methanol, loaded onto a Varian™ SCX column, washed with methanol, subsequently eluted with a 2 M methanol solution of NH₃, concentrated and then purified by preparative TLC (SiO₂, ethyl acetate/methanol = 4:1) to thereby provide (R)-1-(3-amino-4-hydroxybenzyl)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (Compd. No. 2187) (9.6 mg, 59%). The purity was determined by RPLC/MS (86%). ESI/MS m/e 452.3 (M⁺+H, C₂₁H₂₄F₃N₅O₃).

[Example 811] Synthesis of (R)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-[4-chloro-3-(dimethylamino)benzyl]pyrrolidine (Compd. No. 2133)

[0184] NaBH₃CN (38 mg) was added to a mixture of (R)-1-(3-amino-4-chlorobenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (44.9 mg) with methanol (0.95 mL), acetic acid (0.05 mL) and a 37% aqueous solution of HCHO (0.15 mL). The resulting reaction mixture was stirred at 50 °C overnight, cooled

to room temperature and concentrated. A 2 M aqueous solution of NaOH and ethyl acetate were then added to the residue to separate the organic layer. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried and concentrated. The residue was loaded onto a Varian™ SCX column and washed with methanol. The resulting product was eluted with a 2 M methanol solution of NH₃ and concentrated. The residue was dissolved in a 50% concentrated hydrochloric acid/dioxane and stirred at room temperature for 1 hour. The reaction solution was adjusted to pH 10 with a 5 M aqueous solution of NaOH and extracted with ethyl acetate (twice). The extracts were combined, dried over Na₂SO₄, filtered, concentrated and purified by preparative TLC (SiO₂, 20% methanol/ethyl acetate) to thereby afford (R)-3-[[N-2-amino-5-trifluoromethylbenzoyl]glycyl]amino]-1-[4-chloro-3-(dimethylamino)benzyl]pyrrolidine (Compd. No. 2133) (10.9 mg, 28%). The purity was determined by RPLC/MS (95%). ESI/MS m/e 498.3 (M⁺+H, C₂₃H₂₇ClF₃N₅O₂).

[Examples 812 to 814]

[0185] The compounds used in the present invention were synthesized by using the respective starting materials and reactants according to the method of Example 811. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 16.

Table 16

Example	Comps. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
812	2134	C ₂₄ H ₂₈ F ₃ N ₅ O ₄	508.4	19.0	50
813	2135	C ₂₄ H ₃₀ F ₃ N ₅ O ₃	494.4	21.8	50
814	2136	C ₂₄ H ₃₀ F ₃ N ₅ O ₂	478.4	29.2	69

[Example 815] Synthesis of (R)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-(3-methylamino-4-hydroxybenzyl)pyrrolidine (Compd. No. 2158)

[0186] NaBH₃CN (9.2 mg) was added to a mixture of (R)-1-(3-amino-4-hydroxybenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (27.3 mg, 0.049 mmol) with a 37% HCHO solution (4.0 mg, 0.049 mmol), acetic acid (0.10 mL) and methanol (1.3 mL). The resulting reaction mixture was stirred at 60 °C overnight, cooled to room temperature, loaded onto a Varian™ SCX column and washed with methanol (5 mL×2). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (8 mL) and concentrated.

[0187] The resulting residue was dissolved in methanol (1 mL), and a 4 M dioxane solution of HCl (1.0 mL) was added to the solution. The resulting mixture was stirred at room temperature for 3 hours and concentrated. The residue was dissolved in methanol (1 mL), loaded onto a Varian™ column, washed with methanol (5 mL×2), eluted with a 2 M methanol solution of NH₃ (8 mL), concentrated and then purified by preparative TLC (SiO₂) to thereby provide (R)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-(3-methylamino-4-hydroxybenzyl)pyrrolidine (Compd. No. 2158) (4.3 mg, 19%). The purity was determined by RPLC/MS (71%). ESI/MS m/e 480.3 (M⁺+H, C₂₂H₂₆F₃N₅O₃).

[Example 816] Synthesis of (R)-1-(3-acetylamino-4-methoxybenzyl)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (Compd. No. 2152)

[0188] Acetic anhydride (1 mL) was added to a pyridine (1 mL) solution of (R)-1-(3-amino-4-hydroxybenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (50.5 mg). The resulting reaction mixture was stirred at room temperature overnight, and methanol was added to the mixture. The obtained mixture was concentrated, and a 1 M NaOH solution was then added to the concentrate. The resulting mixture was extracted with ethyl acetate, and the organic layer was concentrated and purified by preparative TLC (SiO₂) to thereby afford (R)-1-(3-acetylamino-4-methoxybenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine.

[0189] The resulting (R)-1-(3-acetylamino-4-methoxybenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine was dissolved in a 50% dioxane solution of 6 M hydrochloric acid, and the obtained solution was stirred at room temperature for 2 hours, adjusted to pH 10 with a 5 M NaOH solution and extracted with ethyl acetate. The organic layer was concentrated and purified by preparative TLC (SiO₂) to thereby provide (R)-1-(3-acetylamino-4-methoxybenzyl)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (Compd. No. 2152) (3.7 mg, 8%). The purity was determined by RPLC/MS (100%). ESI/MS m/e 508.3 (M⁺+H, C₂₄H₂₈F₃N₅O₄).

[Examples 817 to 819]

[0190] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 816. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 17.

Table 17

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
817	2150	C ₂₃ H ₂₅ ClF ₃ N ₅ O ₃	512.3	3.8	9
818	2151	C ₂₄ H ₂₆ F ₃ N ₅ O ₅	522.2	3.1	8
819	2153	C ₂₄ H ₂₈ F ₃ N ₅ O ₃	492.3	4.3	10

[Example 820] Synthesis of (R)-3-[[N(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-(benz[d]oxazol-5-yl)pyrrolidine (Compd. No. 2189)

[0191] Triethyl orthoformate (0.20 mL, 3.3 equivalents) and pyridinium p-toluenesulfonate (1.2 mg, 0.4 equivalent) were added to a THF (2 mL) solution of (R)-1-(3-amino-4-hydroxybenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (20 mg) synthesized according to the method of Example 808. The resulting reaction mixture was stirred at room temperature overnight under reflux. The reaction mixture was cooled to room temperature and then concentrated. The obtained residue was dissolved in ethyl acetate, loaded onto a Bond Elut™ Si column, eluted with ethyl acetate/methanol = 4:1 and concentrated.

[0192] The resulting residue was dissolved in ethyl acetate (1.5 mL), and a 4 M dioxane solution of HCl was added to the obtained solution. The resulting solution was stirred overnight, adjusted to pH 10 with a 5 M aqueous solution of NaOH and extracted with ethyl acetate. The obtained extract was concentrated and purified by preparative TLC (SiO₂, ethyl acetate/methanol = 4:1) to thereby provide (R)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-(benz[d]oxazol-5-yl)pyrrolidine (Compd. No. 2189) (0.5 mg, 3%). The purity was determined by RPLC/MS (97%). ESI/MS m/e 462.3 (M⁺+H, C₂₂H₂₂F₃N₅O₃).

[Example 821] Synthesis of (R)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-[benzo[c]thiadiazol-5-yl]pyrrolidine (Compd. No. 2183)

[0193] Methanesulfonyl chloride (0.0042 mL) was added to a mixture of 5-(hydroxymethyl)benzo[c]thiadiazole (8.3 mg, 0.050 mmol) with a (piperidinomethyl)polystyrene (86 mg) and chloroform (1 mL). The resulting mixture was stirred at room temperature for 1.5 hours. Acetonitrile (1 mL) and (R)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzyl)glycyl]amino]pyrrolidine (0.060 mmol) were added to the mixture. The resulting mixture was stirred at 50°C for 3 hours. After cooling to room temperature, phenyl isocyanate (30 mg) was added, and the obtained mixture was stirred at room temperature for 1 hour, loaded onto a Varian™ SCX column and washed with methanol (5 mL) and chloroform (5 mL). The resulting crude product was eluted with a 2 M methanol solution of NH₃ (3 mL) and concentrated.

[0194] The obtained substance was dissolved in dichloromethane (1 mL), and a dichloromethane solution (1 mL) of 1 M chlorotrimethylsilane (1 M) and phenol (1 M) was added to the solution. The resulting solution was stirred at room temperature for 5 hours, loaded onto a Varian™ SCX column and washed with methanol and dichloromethane. The obtained product was eluted with a 2 M methanol solution of NH₃ and concentrated.

[0195] The resulting crude product was purified by preparative TLC (SiO₂, ethyl acetate/methanol = 3:1) to thereby afford (R)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-[benzo[c]thiadiazol-5-yl]pyrrolidine (Compd. No. 2183) (11.5 mg, 58%). The purity was determined by RPLC/MS (86%). ESI/MS m/e 479.2 (M⁺+H, C₂₁H₂₁F₃N₆O₂S).

[Reference Example 6] Synthesis of 4-[[N-(1-(9-fluorenylmethoxycarbonyl)pyrrolidin-3-yl)carbamoylmethyl]aminomethyl]3-methoxyphenyloxymethyl-polystyrene

[0196] Acetic acid (0.3 mL), sodium triacetoxymethylborohydride (1.92 g) and a 4-formyl-3-(methoxyphenyloxymethyl)-polystyrene (1 mmol/g, 200 g) were added to a DMF (65 mL) solution of (R)-1-(9-fluorenylmethoxycarbonyl)-3-glycylaminopyrrolidine hydrochloride (4.38 g, 10 mmol). The resulting mixture was shaken for 2 hours and then filtered. The resin was washed with methanol, DMF, dichloromethane and methanol and dried to thereby provide the objective substance (2.73 g).

[Examples 822 to 912] Solid-phase synthesis of 3-aminopyrrolidines

[0197] Diisopropylethylamine (3.6 mL) was added to a mixture of the corresponding carboxylic acid (1.6 mmol) with HBTU (1.6 mmol) and DMF (6 mL), and the resulting mixture was shaken for 2 minutes. A 4-[[N-(1-(9-fluorenylmethoxycarbonyl)pyrrolidin-3-yl)carbamoylethyl]aminomethyl]-3-methoxyphenyloxymethyl-polystyrene (400 mg, 0.4 mmol) was added, and the obtained mixture was shaken for 1 hour and then filtered. The resin was washed with DMF and dichloromethane and dried.

[0198] A mixture of the resulting resin with piperidine (3.2 mL) and DMF (12.8 mL) was shaken for 10 minutes and then filtered. The resin was washed with DMF and dichloromethane and dried.

[0199] A mixture of NaBH(OAc)₃ (0.25 mmol) with acetic acid (0.025 mL) and DMF (1 mL) was added to the dried resin (0.05 mL). The corresponding aldehyde (2.5 mmol) was added, and the mixture was shaken for 2 hours, then filtered and washed with methanol, a 10% solution of diisopropylethylamine in DMF, DMF, dichloromethane and methanol. A mixture of the resin with water (0.050 mL) and trifluoroacetic acid (0.95 mL) was shaken for 1 hour and then filtered. The resin was washed with dichloromethane and methanol. The filtrate and washings were combined and concentrated. The resulting crude product was loaded onto a Varian™ SCX column and washed with methanol (15 mL). The product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated.

[0200] The obtained products, if necessary, were purified with preparative TLC or HPLC to thereby afford the objective compounds. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 18.

Table 18

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
822	1805	C ₂₁ H ₂₁ BrF ₃ N ₃ O ₂ S	516	13.3	76
823	1806	C ₂₂ H ₂₄ F ₃ N ₃ O ₃ S	468	12.8	81
824	1807	C ₂₂ H ₂₄ F ₃ N ₃ O ₄ S	484	13.7	83
825	1808	C ₂₂ H ₂₄ F ₃ N ₃ O ₄ S	484	14.9	91
826	1809	C ₂₁ H ₂₂ F ₃ N ₃ O ₃ S	454	12.9	84
827	1810	C ₂₂ H ₂₂ F ₃ N ₃ O ₄ S	482	12.9	79
828	1811	C ₂₄ H ₂₆ F ₃ N ₃ O ₂ S	478	12.9	79
829	1812	C ₂₂ H ₂₄ F ₃ N ₃ O ₂ S ₂	484	5.3	32
830	1813	C ₂₃ H ₂₆ F ₃ N ₃ O ₂ S	466	12.8	81
831	1814	C ₂₃ H ₂₄ F ₃ N ₃ O ₃ S	480	9.7	59
832	1815	C ₂₃ H ₂₆ F ₃ N ₃ O ₂ S	466	12.7	80
833	1816	C ₂₄ H ₂₈ F ₃ N ₃ O ₂ S	480	14.4	88
834	1817	C ₂₅ H ₃₀ F ₃ N ₃ O ₂ S	494	14.1	84
835	1818	C ₂₁ H ₂₂ BrF ₂ N ₃ O ₃	482	13.4	82
836	1819	C ₂₂ H ₂₅ F ₂ N ₃ O ₄	434	11.7	79
837	1820	C ₂₂ H ₂₅ F ₂ N ₃ O ₅	450	11.8	77
838	1821	C ₂₂ H ₂₅ F ₂ N ₃ O ₅	450	13.3	87
839	1822	C ₂₁ H ₂₃ F ₂ N ₃ O ₄	420	11.9	83
840	1823	C ₂₂ H ₂₃ F ₂ N ₃ O ₅	448	11.9	78
841	1824	C ₂₄ H ₂₇ F ₂ N ₃ O ₃	444	9.1	60
842	1825	C ₂₂ H ₂₅ F ₂ N ₃ O ₃ S	450	11.3	74
843	1826	C ₂₃ H ₂₇ F ₂ N ₃ O ₃	432	10.8	74
844	1827	C ₂₃ H ₂₅ F ₂ N ₃ O ₄	446	12.7	84
845	1828	C ₂₃ H ₂₇ F ₂ N ₃ O ₃	432	11.7	80
846	1829	C ₂₄ H ₂₉ F ₂ N ₃ O ₃	446	14.3	94

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Table 18 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	847	C ₂₄ H ₂₉ F ₂ N ₃ O ₃	446	10.0	66
	848	C ₂₂ H ₂₈ BrN ₃ O ₃	462	4.8	31
	849	C ₂₃ H ₃₁ N ₃ O ₄	414	10.4	74
10	850	C ₂₃ H ₃₁ N ₃ O ₅	430	12.1	83
	851	C ₂₃ H ₃₁ N ₃ O ₅	430	12.0	82
	852	C ₂₂ H ₂₉ N ₃ O ₄	400	7.9	58
15	853	C ₂₃ H ₂₉ N ₃ O ₅	428	11.1	76
	854	C ₂₅ H ₃₃ N ₃ O ₃	424	13.3	92
	855	C ₂₃ H ₃₁ N ₃ O ₃ S	430	8.7	60
20	856	C ₂₄ H ₃₃ N ₃ O ₃	412	11.3	81
	857	C ₂₄ H ₃₁ N ₃ O ₄	426	12.9	89
	858	C ₂₄ H ₃₃ N ₃ O ₃	413	12.8	91
25	859	C ₂₅ H ₃₅ N ₃ O ₃	426	8.7	60
	860	C ₂₅ H ₃₅ N ₃ O ₃	426	12.2	84
	861	C ₂₆ H ₃₇ N ₃ O ₃	440	11.3	76
30	862	C ₃₁ H ₃₇ BrN ₄ O ₂	577	6.4	30
	863	C ₂₃ H ₂₈ F ₃ N ₃ O ₂ S	480	12.8	81
	864	C ₂₅ H ₃₁ F ₂ N ₃ O ₃	460	12.2	78
35	865	C ₂₇ H ₂₉ N ₃ O ₄	460	6.1	39
	866	C ₂₉ H ₃₁ N ₃ O ₂	454	15.1	98
	867	C ₂₈ H ₃₁ N ₃ O ₂	442	12.7	85
40	868	C ₂₈ H ₃₁ N ₃ O ₂	442	14.3	95
	869	C ₂₈ H ₂₉ N ₃ O ₃	456	3.4	22
	870	C ₂₇ H ₂₉ N ₃ O ₆ S	524	15.4	87
45	871	C ₂₉ H ₃₁ N ₃ O ₄ S	518	15.8	90
	872	C ₂₈ H ₃₁ N ₃ O ₄ S	506	17.0	99
	873	C ₂₈ H ₃₁ N ₃ O ₄ S	506	3.0	17
50	874	C ₂₈ H ₂₉ N ₃ O ₅ S	520	10.0	57
	875	C ₂₀ H ₂₂ Br ₂ N ₄ O ₂	511	9.3*	37
	876	C ₂₁ H ₂₅ BrN ₄ O ₃	461	6.7*	29
55	877	C ₂₁ H ₂₅ BrN ₄ O ₄	477	9.5*	40
	878	C ₂₁ H ₂₅ BrN ₄ O ₄	477	10.0*	42
	879	C ₂₀ H ₂₃ BrN ₄ O ₃	447	7.8*	34
	880	C ₂₁ H ₂₃ BrN ₄ O ₄	475	3.4*	14
	881	C ₂₁ H ₂₅ BrN ₄ O ₂ S	477	3.9*	16
	882	C ₂₂ H ₂₅ BrN ₄ O ₃	473	6.4*	27
	883	C ₂₃ H ₂₉ BrN ₄ O ₂	472	7.0*	29

Note: * indicates "yield (mg) of trifluoroacetate".

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Table 18 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
884	1867	C ₂₃ H ₂₉ BrN ₄ O ₂	473	7.6*	32
885	1868	C ₂₄ H ₃₁ BrN ₄ O ₂	487	9.1*	37
886	1869	C ₂₀ H ₂₂ BrIN ₄ O ₂	557	8.9*	33
887	1870	C ₂₁ H ₂₅ IN ₄ O ₃	509	9.2*	37
888	1871	C ₂₁ H ₂₅ IN ₄ O ₄	525	6.3*	25
889	1872	C ₂₁ H ₂₅ IN ₄ O ₄	525	5.9*	23
890	1873	C ₂₀ H ₂₃ IN ₄ O ₃	495	7.7*	31
891	1874	C ₂₁ H ₂₃ IN ₄ O ₄	523	8.2*	32
892	1875	C ₂₃ H ₂₇ IN ₄ O ₂	519	6.7*	26
893	1876	C ₂₁ H ₂₅ IN ₄ O ₂	525	4.3*	17
894	1877	C ₂₂ H ₂₇ IN ₄ O ₂	507	7.9*	32
895	1878	C ₂₂ H ₂₅ IN ₄ O ₃	521	8.4*	33
896	1879	C ₂₃ H ₂₉ IN ₄ O ₂	521	8.2*	32
897	1880	C ₂₃ H ₂₉ IN ₄ O ₂	521	8.1*	32
898	1881	C ₂₄ H ₃₁ IN ₄ O ₂	535	8.6*	33
899	1882	C ₂₀ H ₂₂ BrN ₅ O ₄	476	5.3*	22
900	1883	C ₂₁ H ₂₅ N ₅ O ₅	428	5.7*	26
901	1884	C ₂₁ H ₂₅ N ₅ O ₆	444	8.2*	36
902	1885	C ₂₁ H ₂₅ N ₅ O ₆	444	5.0*	22
903	1886	C ₂₀ H ₂₃ N ₅ O ₅	414	8.7*	40
904	1887	C ₂₁ H ₂₃ N ₅ O ₆	442	7.8*	34
905	1888	C ₂₃ H ₂₇ N ₅ O ₄	438	5.6*	25
906	1889	C ₂₁ H ₂₅ N ₅ O ₄ S	444	13.2*	58
907	1890	C ₂₂ H ₂₇ N ₅ O ₄	426	11.3*	51
908	1891	C ₂₂ H ₂₅ N ₅ O ₅	440	7.4*	33
909	1892	C ₂₂ H ₂₇ N ₅ O ₄	426	5.5*	25
910	1893	C ₂₃ H ₂₉ N ₅ O ₄	440	5.7*	25
911	1894	C ₂₃ H ₂₉ N ₅ O ₄	440	9.4*	41
912	1895	C ₂₄ H ₃₁ N ₅ O ₄	455	8.5*	37

Note: * indicates "yield (mg) of trifluoroacetate".

[Reference Example 7] Synthesis of 2-carbamoyl-1-(4-chlorobenzyl)pyrrolidine

[0201] Triethylamine (7.45 mL) and 4-chlorobenzyl chloride (3.88 g, 24.1 mmol) were added to an acetonitrile (35 mL) solution of dl-prolinamide hydrochloride (2.5 g, 21.8 mmol). The resulting reaction mixture was stirred at 0°C for 4 hours and subsequently stirred at 25 °C for 16 hours. The resulting mixture was diluted with dichloromethane (20 mL) and washed with water (30 mL×3). The organic layer was dried (over MgSO₄) and concentrated. The obtained crude product was purified by chromatography (SiO₂, methanol-dichloromethane) to thereby provide 2-carbamoyl-1-(4-chlorobenzyl)pyrrolidine (5.21 g, 81%).

[Reference Example 8] Synthesis of 2-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine

[0202] 2-Carbamoyl-1-(4-chlorobenzyl)pyrrolidine was dissolved in 1 M BH₃-THF (9.4 mL), and the resulting solution was heated at 70 °C. A 1 M BH₃-THF (0.5 equivalent) was further added twice after 16 hours and 25 hours. After 40 hours, a 1 M hydrochloric acid was added, and the resulting mixture was refluxed for 3 hours. A 3 M hydrochloric acid (6 mL) was added, and the reaction product was stirred for another 3 hours with heating, then cooled to 25°C, alkalized with a 6 M aqueous solution of NaOH and extracted with dichloromethane (4×15 mL). The obtained crude product was purified by chromatography (SiO₂, PrOH/H₂O/NH₄OH = 8:1:1) to thereby afford 2-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine (1.21 g, 86%).

[0203] Furthermore, optically active (S)- 2-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine and (R)-2-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine were synthesized by using the respective corresponding starting materials and reactants according to the above method.

[0204] (S)-2-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine: ¹H NMR (CDCl₃, 400MHz) δ 1.40-1.80 (m, 5 H), 1.80-1.95 (m, 1 H), 2.12-2.21 (m, 1 H), 2.48-2.65 (m, 1 H), 2.66-2.78 (m, 2 H), 2.85-2.95 (m, 1 H), 3.26 (d, J = 13.2 Hz, 1 H), 3.93 (d, J = 13.2, 1 H), 7.20-7.40 (m, 4 H).

[0205] (R)-2-(Aminomethyl)-1-(4-chlorobenzyl)pyrrolidine exhibited the same ¹H NMR as that of the (S)-isomer.

[Example 913] Synthesis of 2-[[N(benzoylleucyl)aminomethyl]-1-(4-chlorobenzyl)pyrrolidine (Compd. No. 344)

[0206] EDCI (23 mg), HOBt (16.2 mg) and triethylamine (15.2 μL) were added to a chloroform (1 mL) solution of 2-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine (22.5 mg, 0.10 mmol) and dl-benzoylleucine (0.12 mL), and the resulting mixture was stirred at 25 °C for 16 hours. The reaction mixture was diluted with dichloromethane (0.5 mL), washed with a 2 M aqueous solution of NaOH (0.75 mL×2), filtered through a PTFE membrane, thereby dried and concentrated to provide 2-[[N(benzoylleucyl)aminomethyl]-1-(4-chlorobenzyl)pyrrolidine (Compd. No. 344) (74 mg, quantitative). The purity was determined by RPLC/MS (85%). ESI/MS m/e 442 (M⁺+H, C₂₃H₃₂ClN₃O₂).

[Examples 914 to 933]

[0207] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 913. The obtained products, if necessary, were purified by chromatography (HPLC-C₁₈, acetonitrile/H₂O/TFA), and the objective compounds were obtained as TFA salts. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 19. Compd. Nos. 339 and 340 exhibited the following ¹H NMR, respectively.

Table 19

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
914	330	C ₂₁ H ₂₄ ClN ₃ O ₂	386	75*	Q
915	331	C ₂₂ H ₂₆ Cl ₃ O ₂	400	44*	70
916	332	C ₂₄ H ₃₀ ClN ₃ O ₅	476	57	Q
917	333	C ₂₀ H ₂₃ ClN ₄ O ₂	387	40	Q
918	334	C ₂₂ H ₂₆ ClN ₃ O ₂	400	68	Q
919	335	C ₂₁ H ₂₃ ClN ₄ O ₄	431	73	Q
920	336	C ₂₂ H ₂₃ ClF ₃ N ₃ O ₂	454	75	Q
921	337	C ₂₂ H ₂₆ ClN ₃ O ₂	400	68	Q
922	338	C ₂₂ H ₂₆ ClN ₃ O ₂	400	70	Q
923	341	C ₂₂ H ₂₆ ClN ₃ O ₂	400	80*	Q
924	342	C ₂₂ H ₂₆ ClN ₃ O ₂	400	68	Q
925	343	C ₂₄ H ₃₀ ClN ₃ O ₂	428	63	Q
926	345	C ₂₃ H ₂₇ ClN ₂ O ₂	399	68*	Q

Notes: * indicates "yield (mg) of trifluoroacetate".
Q means "Quantitative".

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Table 19 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
927	346	C ₂₃ H ₂₆ ClFN ₂ O ₃	433	51	Q
928	347	C ₂₄ H ₂₉ ClN ₂ O ₂	413	47	Q
929	348	C ₂₃ H ₂₇ ClN ₂ O ₂	399	26	Q
930	349	C ₂₁ H ₂₅ ClN ₂ O ₃ S	421	42	Q
931	350	C ₂₆ H ₃₃ ClN ₂ O ₃	457	12.4	54
932	351	C ₂₂ H ₂₆ ClN ₃ O ₃	416	34	81
933	352	C ₂₂ H ₂₅ Cl ₂ N ₃ O ₃	450	51	Q

[0208] [Example 934] Compd. No. 339: 82%; ¹H NMR (CDCl₃) δ 1.52-1.75 (m, 4 H), 1.84-1.95 (m, 1 H), 2.10-2.20 (m, 1 H), 2.67-2.78 (m, 1 H), 2.80-2.90 (m, 1 H), 3.10-3.20 (m, 1 H), 3.25 (d, J = 13.1 Hz, 1 H), 3.50-3.60 (m, 1 H), 3.89 (d, J = 13.1 Hz, 1 H), 4.28-4.20 (m, 2 H), 7.00-7.05 (m, 1 H), 7.12-7.29 (m, 4 H), 7.51 (t, J = 7.8 Hz, 1 H), 7.74 (d, J = 7.8 Hz, 1 H), 7.99 (d, J = 7.8 Hz, 1 H), 8.10-8.27 (m, 2 H).

[0209] [Example 935] Compd. No. 340: 68%; ¹H NMR (CDCl₃) δ 1.55-1.73 (m, 4 H), 1.86-1.97 (m, 1 H), 2.12-2.21 (m, 1 H), 2.67-2.76 (m, 1 H), 2.86-2.93 (m, 1 H), 3.14-3.21 (m, 1 H), 3.27 (d, J = 13.1 Hz, 1 H), 3.52-3.59 (m, 1 H), 3.89 (d, J = 13.1 Hz, 1 H), 4.09-4.21 (m, 2 H), 7.00-7.07 (m, 1 H), 7.12-7.30 (m, 4 H), 7.50 (t, J = 7.8 Hz, 1 H), 7.73 (d, J = 7.8 Hz, 1 H), 8.01 (d, J = 7.8 Hz, 1 H), 8.10-8.25 (m, 2 H).

[Reference Example 9] Synthesis of 3-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine

[0210] A 0.5 M dioxane solution of ammonia (60 mL, 30 mmol) was added to a mixture of 4-carboxy-1-(4-chlorobenzyl)pyrrolidin-2-one (5.05 g, 20 mmol) with EDCI (2.85 g, 22 mmol), HOBt (2.97 g, 22 mmol) and dichloromethane (100 mL). The resulting reaction mixture was stirred at room temperature for 15 hours and washed with 2 M HCl (three times) and a 2 M aqueous solution of NaOH (100 mL×4). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to thereby provide 4-carbamoyl-(4-chlorobenzyl)pyrrolidin-2-one (1.49 g) as a colorless solid.

[0211] A 1.0 M THF solution of BH₃ (25 mL) was added to a THF (15 mL) solution of 4-carbamoyl-1-(4-chlorobenzyl)pyrrolidin-2-one (1.49 g). The resulting reaction mixture was stirred for 15 hours and cooled to room temperature. The solvent was then removed under reduced pressure. Water (30 mL) and concentrated hydrochloric acid (10 mL) were added, and the mixture was stirred at 100 °C for 2 hours and at room temperature for 1 hour. A 2 M aqueous solution of NaOH (100 mL) was added, and the obtained mixture was extracted with ethyl acetate (50 mL×3). The organic layers were combined, dried over K₂CO₃, filtered, concentrated and purified by column chromatography (SiO₂, 15% methanol-5% triethylamine/dichloromethane) to thereby afford 3-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine (860 mg, 19%) as a colorless oil.

[Reference Example-10] Synthesis of 1-(4-chlorobenzyl)-3-[(glycylamino)methyl]pyrrolidine

[0212] A mixture of 3-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine (860 mg, 3.8 mmol) with triethylamine (5.7 mmol), N-tert-butoxycarbonylglycine (704 mg), EDCI (594 mg), HOBt (673 mg) and dichloromethane (20 mL) was stirred at room temperature for 15 hours, and dichloromethane (50 mL) was added to the mixture. The resulting solution was washed with a 2 M aqueous solution of NaOH (50 mL×2), dried over anhydrous sodium sulfate, filtered and concentrated to thereby provide 3-[[N-(tert-butoxycarbonyl)glycyl]aminomethyl]-1-(4-chlorobenzyl)pyrrolidine (1.31 g, 90%).

[0213] A 4 M dioxane solution of HCl (5 mL) was added to a methanol (10 mL) solution of 3-[[N-tert-butoxycarbonyl]glycyl]aminomethyl]-1-(4-chlorobenzyl)pyrrolidine (804 mg, 2.11 mmol). The resulting solution was stirred at room temperature for 3.5 hours and then concentrated, and a 1 M aqueous solution of NaOH (20 mL) was added. The resulting mixture was extracted with dichloromethane (20 mL×3), and the extracts were combined, dried over sodium sulfate and concentrated to thereby afford 1-(4-chlorobenzyl)-3-[(glycylamino)methyl]pyrrolidione (599 mg, 100%). The purity was determined by RPLC/MS (100%). ESI/MS m/e 282.2 (M⁺+H, C₁₄H₂₀ClN₃O).

[Example 936] Synthesis of 3-[[N-[3-trifluoromethylbenzoyl]glycyl]aminomethyl]-1-(4-chlorobenzyl)pyrrolidine (Compd. No. 1463)

[0214] A dichloromethane (0.2 mL) solution of 3-(trifluoromethyl)benzoyl chloride (0.058 mmol) was added to a mix-

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ture of a chloroform (0.2 mL) solution of 1-(4-chlorobenzyl)-3-[(glycylamino)methyl]pyrrolidine (0.050 mmol) with a dichloromethane (1 mL) solution of a piperidinomethylpolystyrene (60 mg). The resulting reaction mixture was stirred at room temperature for 2.5 hours, and methanol (0.30 mL) was then added. The reaction mixture was loaded onto a Varian™ SCX column and washed with methanol (15 mL). The obtained crude product was eluted with a methanol (5 mL) solution of 2 M NH₃ and concentrated to thereby provide 3-[(N-[3-trifluoromethylbenzoyl]glycyl)aminomethyl]-1-(4-chlorobenzyl)pyrrolidine (Compd. No. 1463) (22.4 mg, 99%). The purity was determined by RPLC/MS (97%). ESI/MS m/e 454.2 (M⁺+H, C₂₂H₂₃ClF₃N₃O₂).

[Examples 937 to 944]

[0215] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 936. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 20.

Table 20

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
937	1464	C ₂₂ H ₂₃ ClF ₃ N ₃ O ₃	470.0	21.0	89
938	1465	C ₂₃ H ₂₂ ClF ₆ N ₃ O ₂	522.0	24.5	94
939	1466	C ₂₁ H ₂₃ BrClN ₃ O ₂	466.0	20.8	90
940	1467	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	19.6	93
941	1468	C ₂₁ H ₂₃ ClN ₄ O ₄	431.2	19.5	91
942	1469	C ₂₂ H ₂₂ ClF ₄ N ₃ O ₂	472.0	21.8	92
943	1470	C ₂₁ H ₂₂ Cl ₃ N ₃ O ₂	456.0	22.1	97
944	1471	C ₂₁ H ₂₂ ClF ₂ N ₃ O ₂	422.0	20.9	99

[Example 945] Synthesis of 3-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(4-chlorobenzyl)pyrrolidine (Compd. No. 1506)

[0216] 2-Amino-4,5-difluorobenzoic acid (0.060 mmol), diisopropylcarbodiimide (0.060 mmol) and HOBt (0.060 mmol) were added to a solution of 1-(4-chlorobenzyl)-3-[(glycylamino)methyl]pyrrolidine (0.050 mmol) in chloroform (1.35 mL) and tert-butanol (0.05 mL). The resulting reaction mixture was stirred at room temperature for 19 hours, then loaded onto a Varian™ SCX column and washed with methanol/chloroform = 1:1 (10 mL) and methanol (10 mL). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated to thereby afford 3-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(4-chlorobenzyl)pyrrolidine (Compd. No. 1506) (22.0 mg, quantitative). The purity was determined by RPLC/MS (92%). ESI/MS m/e 437 (M⁺+H, C₂₁H₂₃ClF₂N₄O₂).

[Examples 946 to 952]

[0217] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 945. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 21.

Table 21

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
946	1506	C ₂₁ H ₂₄ BrClN ₄ O ₂	481	20.6	86
947	1507	C ₂₁ H ₂₄ FCIN ₄ O ₂	419	21.7	Q
948	1509	C ₂₇ H ₂₈ ClN ₃ O ₂	462	26.5	Q
949	1510	C ₂₁ H ₂₄ ClIN ₄ O ₂	527	22.0	84
950	1511	C ₁₉ H ₂₁ BrClN ₃ O ₂ S	472	23.7	Q
951	1512	C ₂₁ H ₂₄ Cl ₂ N ₄ O ₂	435	22.3	Q

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Table 21 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
952	1513	C ₂₇ H ₂₈ ClN ₃ O ₄ S	526	24.6	94
Note: Q means "Quantitative".					

[Reference Example 11] Synthesis of 1-(4-chlorobenzyl)nipecotic acid

[0218] 4-Chlorobenzyl chloride (6.42 g, 39.9 mmol) and ⁱPr₂NEt (7.74 g, 40.0 mmol) were added to an acetonitrile (15 mL) solution of ethyl nipecotate (6.29 g, 40.0 mmol). The resulting reaction mixture was stirred at 70 °C for 1.5 hours, and the solvent was removed under reduced pressure. A saturated aqueous solution of NaHCO₃ (50 mL) was added to the residue, and the resulting mixture was extracted with ethyl acetate (100 mL). The organic layer was washed with a saturated aqueous solution of NaHCO₃ and dried over Na₂SO₄. The solvent was removed under reduced pressure to thereby provide ethyl 1-(4-chlorobenzyl)nipecotate as a reddish yellow oil. (11.0 g, 97.8%). The resulting oil was used without purification. The purity was determined by RPLC/MS (97%). ESI/MS m/e 382.2 (M⁺+H, C₁₅H₂₁ClNO₂).

[0219] An H₂O (25 mL) solution of LiOH (1.66 g) was added to a THF (60 mL) solution of ethyl 1-(4-chlorobenzyl)nipecotate. The resulting reaction mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure to provide an amorphous solid. The obtained crude product was purified by column chromatography (SiO₂, 50% methanol-dichloromethane) to afford 1-(4-chlorobenzyl)nipecotic acid (9.75 g, 98.2%) as an off-white amorphous solid. The purity was determined by RPLC/MS (>95%). ESI/MS m/e 254.0 (M⁺+H, C₁₃H₁₇ClNO₂).

[Reference Example 12] Synthesis of 1-(4-chlorobenzyl)-3-[(tert-butoxycarbonyl)amino]piperidine

[0220] Triethylamine (3.38 g) and activated 3 Å molecular sieve (30 g) were added to a ^tBuOH (500 mL) solution of 1-(4-chlorobenzyl)nipecotic acid (7.06 g, 27.8 mmol). Diphenylphosphoryl azide (8.58 g) was added, and the resulting reaction mixture was stirred under reflux for 18 hour and cooled. The solvent was removed under reduced pressure. The obtained residue was then dissolved in ethyl acetate (500 mL), and the organic layer was washed with a saturated aqueous solution of NaHCO₃ (100 mL×2) and brine (50 mL), then dried (over Na₂SO₄) and concentrated under reduced pressure. The obtained crude product was purified by chromatography (SiO₂, 25% ethyl acetate-hexane) to provide 1-(4-chlorobenzyl)-3-[(tert-butoxycarbonyl)amino]piperidine (2.95 g, 32.6%) as a white crystalline solid. ¹H NMR (CDCl₃, 300MHz) δ 1.4-1.75 (br, 4 H), 2.2-2.7 (br, 4 H), 3.5 (br, 2 H), 3.8 (br, 4 H), 7.3 (br, 4 H). The purity was determined by RPLC/MS (>99%). ESI/MS m/e 269.2 (M⁺+H- 56, C₁₇H₂₆ClN₂O₂).

[Reference Example 13] Synthesis of 3-amino-1-(4-chlorobenzyl)piperidine

[0221] To a methanol (25 mL) solution of 1-(4-chlorobenzyl)-3-[(tert-butoxycarbonyl)amino]piperidine (2.55 g, 7.85 mmol), was added 1M HCl-Et₂O (50 mL). The resulting reaction mixture was stirred at 25 °C for 15 hours, and the solvent was removed under reduced pressure to afford 3-amino 1-(4-chlorobenzyl)piperidine dihydrochloride as an amorphous solid (2.49 g, quantitative). The purity was determined by RPLC/MS (>95%). ESI/MS m/e 225.2 (M⁺+H, C₁₂H₁₈ClN₂).

[Example 953] Synthesis of 1-(4-chlorobenzyl)-3-[[N-(3-methylbenzoyl)glycyl]amino]piperidine (Compd. No. 355)

[0222] N-(3-Methylbenzoyl)glycine (10.6 mg, 0.055 mmol), EDCI (10.5 mg) and 1-hydroxybenzotriazole hydrate (7.4 g) were added to a chloroform (2.5 mL) solution of 1-(4-chlorobenzyl)-3-aminopiperidine dihydrochloride (1.49 mg, 0.050 mmol) and triethylamine (15.2 mg). The resulting reaction mixture was stirred at 25 °C for 16 hours and washed with a 2 N aqueous solution of NaOH (2 mL×2) and brine (1 mL). After filtration through a PTFE membrane, the solvent was removed under reduced pressure to provide 1-(4-chlorobenzyl)-3-[[N-(3-methylbenzoyl)glycyl]amino]piperidine (Compd. No. 355) (17.4 mg, 87%). The purity was determined by RPLC/MS (97%). ESI/MS m/e 400.0 (M⁺+H, C₂₂H₂₆ClN₃O₂).

[Examples 954 to 982]

[0223] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 953. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 22. The Compd. No. 358 exhibited the following ¹H NMR.

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Table 22

Example	Compd. No	Molecular Formula	ESI/MS m/e	Yield (mg)	Yeld (%)
954	354	C ₂₁ H ₂₄ ClN ₃ O ₂	386	16.1	83
955	356	C ₂₀ H ₂₃ ClN ₄ O ₂	387	19.4	100
956	357	C ₂₂ H ₂₆ ClN ₃ O ₂	400	16.8	84
957	359	C ₂₂ H ₂₆ ClN ₃ O ₂	400	8.9	17
958	360	C ₂₂ H ₂₅ ClN ₄ O ₄	445	25.6	Q
959	361	C ₂₃ H ₂₇ ClN ₂ O ₂	399	15.5	29
960	362	C ₂₄ H ₂₉ ClN ₂ O ₃	429	12.4	58
961	363	C ₂₁ H ₂₅ ClN ₂ O ₂ S	405	22.2	Q
962	364	C ₂₄ H ₂₉ ClN ₂ O ₄	445	20.7	93
963	365	C ₂₄ H ₂₉ ClN ₂ O ₂	413	15.6	75
964	366	C ₂₃ H ₂₆ ClFN ₂ O ₃	433	21.6	100
965	367	C ₂₃ H ₂₇ ClN ₂ O ₂	399	11.9	60
966	368	C ₂₂ H ₂₅ ClN ₂ O ₂	385	16.0	83
967	369	C ₂₂ H ₂₄ Cl ₂ N ₂ O ₂	419	13.9	60
968	370	C ₂₆ H ₃₃ ClN ₂ O ₃	457	15.9	54
969	371	C ₂₅ H ₃₁ ClN ₂ O ₃	443	19.6	84
970	372	C ₂₁ H ₂₅ ClN ₂ O ₃ S	421	23.0	Q
971	373	C ₂₃ H ₂₈ ClN ₃ O ₂	414	19.1	92
972	374	C ₂₄ H ₃₀ ClN ₃ O ₃	444	18.6	84
973	375	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₂	448	18.0	80
974	376	C ₂₄ H ₃₀ ClN ₃ O ₃	444	19.6	88
975	377	C ₂₅ H ₃₁ Cl ₂ N ₃ O ₂	476	20.7	87
976	378	C ₂₇ H ₃₃ ClFN ₃ O ₂	486	23.9	98
977	379	C ₂₅ H ₃₀ ClN ₃ O ₃	456	33.3	Q
978	380	C ₂₄ H ₃₀ ClN ₃ O ₂	428	9.8	46
979	381	C ₂₁ H ₂₆ ClN ₃ O ₃ S	436	10.3	47
980	382	C ₂₂ H ₂₆ ClN ₃ O ₃	416	24.4	Q
981	383	C ₂₂ H ₂₅ Cl ₂ N ₃ O ₃	450	27.5	Q
Note: Q means "Quantitative".					

[0224] [Example 982] Compd. No. 358: 88%; ¹H NMR (CDCl₃) δ 1.53-1.75 (m, 4 H), 2.12-2.20 (m, 1 H), 2.37-2.50 (m, 2 H), 2.53-2.61 (m, 1 H), 3.38-3.50 (m, 2 H), 2.53-2.61 (m, 1 H), 3.38-3.50 (m, 2 H), 4.06-4.20 (m, 3 H), 7.10-7.13 (m, 1 H), 7.18-7.30 (m, 4 H), 7.59 (t, J = 7.8 Hz, 1 H), 7.79 (d, J = 7.8 Hz, 1 H), 8.01 (d, J = 7.8 Hz, 1 H), 8.11(s, 1 H).

[Reference Example 14] Synthesis of 1-benzyl-4-[[N-(tert-butoxycarbonyl)glycyl]amino]piperidine

[0225] N-(tert-Butoxycarbonyl)glycine (3.48 g, 20 mmol), EDCI (4.02 g, 21 mmol) and HOBt (2.83 g, 21 mmol) were added to a dichloromethane (40 mL) solution of 4- amino-1-benzylpiperidine (3.80 g, 20 mmol). The resulting reaction mixture was stirred at room temperature for 12 hours, and a 2 M solution of NaOH was then added. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (20 mL×2). The organic layers were combined, washed with water (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography (SiO₂, ethyl acetate/methanol/triethylamine = 85:

12:3) to afford 1-benzyl-4-[[N-(tert-butoxycarbonyl)glycyl]amino]piperidine (6.59 g, 95%).

[Reference Example 15] Synthesis of 1-benzyl-4-(glycylamino)piperidine

[0226] A 4 M dioxane solution of HCl was added to a methanol (80 mL) solution of 1-benzyl-4-[N-(tert-butoxycarbonyl)glycyl]aminopiperidine (6.59 g). The resulting solution was stirred at room temperature for 2 hours and concentrated. A 2 M aqueous solution of NaOH (20 mL) was then added to the solution. The resulting mixture was extracted with dichloromethane (40 mL). The extracts were combined, dried over anhydrous sodium sulfate and concentrated. The obtained crude product was purified by column chromatography (SiO₂, ethyl acetate/methanol/triethylamine = 85:12:3) to thereby provide 1-benzyl-4-(glycylamino)piperidine (3.91 g, 83%). ¹H NMR (CDCl₃, 400 MHz) δ 1.47-1.59 (m, 2 H), 1.59 (br, 2 H), 1.76-1.96 (m, 2 H), 2.10-2.19 (m, 2 H), 2.75-2.87 (m, 2 H), 3.29 (s, 2 H), 3.50 (s, 2 H), 3.65-3.89 (m, 1 H), 7.15-7.23 (m, 1 H), 7.23-7.33 (m, 5 H).

[0227] Other 4-acylamino-1-benzylpiperidines were synthesized by using the respective corresponding starting materials and reactants according to the methods of Reference Examples 14 and 15.

[0228] 4-(β-alanyl-amino)-1-benzylpiperidine: 2.46 g, 51% (two steps)

[0229] 1-benzyl-4-((S)-leucylamino)piperidine: 1.78 g, 74% (two steps) and 1-benzyl-4-((R)-leucylamino)piperidine: 1.48 g, 61% (two steps).

[Example 983] Synthesis of 4-(N-benzoylglycyl)amino-1-benzylpiperidine (Compd. No. 386)

[0230] A chloroform (0.4 mL) solution of benzoyl chloride (0.060 mmol) was added to a chloroform (1.0 mL) solution of 1-benzyl-4-(glycylamino)piperidine (0.050 mmol) and triethylamine (0.070 mmol). The resulting reaction mixture was shaken at room temperature for 12 hours, and an (aminomethyl)polystyrene resin (1.04 mmol/g, 50 mg, 50 mmol) was added to the mixture. The obtained mixture was shaken at room temperature for 12 hours. The resulting reaction mixture was filtered, and the resin was washed with dichloromethane (0.5 mL). The filtrate and washings were combined, and dichloromethane (4 mL) was added. The solution was washed with a 2 M aqueous solution of NaOH (0.5 mL) to provide 4-(N-benzoylglycyl)amino-1-benzylpiperidine (Compd. No. 386) (11.3 mg, 64%). The purity was determined by RPLC/MS (94%). ESI/MS m/e 352.0 (M⁺+H, C₂₁H₂₅N₃O₂).

[Examples 984 to 1034]

[0231] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 983. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 23.

Table 23

Example	Compd. No	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
984	384	C ₂₂ H ₂₆ ClN ₃ O ₂	400	60.0	Q
985	385	C ₂₁ H ₂₃ ClN ₄ O ₄	431	58.7	91
986	387	C ₂₅ H ₂₇ N ₃ O ₂	402.5	15.5	77
987	388	C ₂₁ H ₂₄ N ₄ O ₄	397.0	16.2	82
988	389	C ₂₃ H ₂₇ N ₃ O ₄	410.0	16.2	79
989	390	C ₂₂ H ₂₄ F ₃ N ₃ O ₂	420.0	17.4	83
990	391	C ₂₂ H ₂₃ F ₄ N ₃ O ₂	438.0	18.4	84
991	392	C ₂₂ H ₂₄ F ₃ N ₃ O ₃	436.0	17.1	79
992	393	C ₂₁ H ₂₄ BrN ₃ O ₂	430.0	18.0	84
993	394	C ₂₁ H ₂₄ ClN ₃ O ₂	386.0	16.4	85
994	395	C ₂₁ H ₂₄ BrN ₃ O ₂	430.0	17.2	80
995	396	C ₂₁ H ₂₃ F ₂ N ₃ O ₂	388.0	15.1	78
996	397	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	11.7	56
997	398	C ₂₂ H ₂₇ N ₃ O ₂	366.0	13.1	72

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Table 23 (continued)

Example	Compd. No	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	998	C ₂₆ H ₂₉ N ₃ O ₂	416.0	15.8	76
	999	C ₂₂ H ₂₆ N ₄ O ₄	411.0	17.4	85
	1000	C ₂₄ H ₂₉ N ₃ O ₄	424.0	16.9	80
10	1001	C ₂₃ H ₂₆ F ₃ N ₃ O ₂	434.0	17.7	82
	1002	C ₂₃ H ₂₅ F ₄ N ₃ O ₂	452.0	18.6	82
	1003	C ₂₃ H ₂₆ F ₃ N ₃ O ₃	450.0	17.8	79
15	1004	C ₂₂ H ₂₆ BrN ₃ O ₂	444.0	17.9	81
	1005	C ₂₂ H ₂₆ ClN ₃ O ₂	400.0	15.5	78
	1006	C ₂₂ H ₂₆ BrN ₃ O ₂	444.0	17.8	80
20	1007	C ₂₂ H ₂₅ F ₂ N ₃ O ₂	402.0	15.6	78
	1008	C ₂₂ H ₂₅ Cl ₂ N ₃ O ₂	434.0	17.6	81
	1009	C ₂₅ H ₃₃ N ₃ O ₂	408.0	16.2	79
25	1010	C ₂₉ H ₃₅ N ₃ O ₂	458.5	18.8	82
	1011	C ₂₅ H ₃₂ N ₄ O ₄	453.0	19.4	86
	1012	C ₂₇ H ₃₅ N ₃ O ₄	466.0	19.8	85
30	1013	C ₂₆ H ₃₂ F ₃ N ₃ O ₂	476.0	20.2	85
	1014	C ₂₆ H ₃₁ F ₄ N ₃ O ₂	494.0	20.5	83
	1015	C ₂₆ H ₃₂ F ₃ N ₃ O ₃	492.0	19.5	79
35	1016	C ₂₅ H ₃₂ BrN ₃ O ₂	486.0	19.1	79
	1017	C ₂₅ H ₃₂ ClN ₃ O ₂	442.0	17.7	80
	1018	C ₂₅ H ₃₂ BrN ₃ O ₂	486.0	20.3	83
40	1019	C ₂₅ H ₃₁ F ₂ N ₃ O ₂	444.0	18.6	84
	1020	C ₂₅ H ₃₁ Cl ₂ N ₃ O ₂	476.0	19.4	81
	1021	C ₂₅ H ₃₃ N ₃ O ₂	408.0	14.4	71
45	1022	C ₂₉ H ₃₅ N ₃ O ₂	458.0	16.4	72
	1023	C ₂₅ H ₃₂ N ₄ O ₄	453.0	18.1	80
	1024	C ₂₇ H ₃₅ N ₃ O ₄	466.0	16.4	70
50	1025	C ₂₆ H ₃₂ F ₃ N ₃ O ₂	476.0	17.3	73
	1026	C ₂₆ H ₃₁ F ₄ N ₃ O ₂	494.0	18.8	76
	1027	C ₂₆ H ₃₂ F ₃ N ₃ O ₃	492.0	18.4	75
55	1028	C ₂₅ H ₃₂ BrN ₃ O ₂	486.0	17.9	74
	1029	C ₂₅ H ₃₂ ClN ₃ O ₂	442.0	15.7	71
	1030	C ₂₅ H ₃₂ BrN ₃ O ₂	486.0	17.7	73
	1031	C ₂₅ H ₃₁ F ₂ N ₃ O ₂	444.0	16.6	75
	1032	C ₂₅ H ₃₁ Cl ₂ N ₃ O ₂	476.0	18.7	78
	1033	C ₂₂ H ₂₃ ClF ₃ N ₃ O ₂	454	32.5*	53
	1034	C ₂₁ H ₂₄ ClN ₃ O ₂	386	55.2*	Q

Notes: * indicates "yield (mg) of trifluoroacetate".
Q means "Quantitative".

[Reference Example 16] Synthesis of 3-carbamoyl-1-(4-chlorobenzyl)piperidine

[0232] Triethylamine (7.0 mL, 50 mmol) and 4-chlorobenzyl chloride (8.05 g, 50 mmol) were added to a solution of nipecotamide (6.40 g, 50 mmol) in acetonitrile (150 mL) and ethanol (20 mL). The resulting reaction mixture was stirred at 50 °C for 16 hours and cooled to room temperature. A saturated aqueous solution of NaHCO₃ (50 mL) and water (150 mL) were then added, and the resulting mixture was extracted with ethyl acetate (150 mL×3). The extracts were washed with brine, dried over Na₂SO₄ and concentrated to afford a light-red solid. The obtained crude solid was washed with ether (100 mL) to provide 3-carbamoyl-1-(4-chlorobenzyl)piperidine (6.98 g, 54%).

[Reference Example 17] Synthesis of 3-(aminomethyl)-1-(4-chlorobenzyl)piperidine

[0233] 3-Carbamoyl-1-(4-chlorobenzyl)piperidine (3.80 g, 15 mmol) was dissolved in THF (30 mL), and 1 M BH₃-THF (9.4 mL) was added to the obtained solution. The resulting mixture was stirred at 70 °C for 15 hours. After cooling to 0 °C, a 2 M hydrochloric acid (50 mL) was added, and the mixture was stirred at room temperature for another 3 hours, basicified with an 4 M aqueous solution of NaOH and extracted with ethyl acetate (100 mL×3). The extracts were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The obtained crude product was purified by column chromatography (SiO₂, ethyl acetate/ethanol/triethylamine = 80:15:5) to thereby provide 3-(aminomethyl)-1-(4-chlorobenzyl)piperidine (2.05 g, 55%). ¹H NMR (CDCl₃, 400MHz) δ 1.00-1.09 (m, 1 H), 1.50-1.87 (m, 7 H), 1.97-2.06 (m, 1 H), 2.65-2.77 (m, 2 H), 3.16-3.26 (m, 2 H), 3.32 (s, 2 H), 3.40 (d, J = 13.3 Hz, 1 H), 3.49 (d, J = 13.3 Hz, 1 H), 7.22-7.33 (m, 5 H).

[Example 1035] Synthesis of 3-[(N-benzoylglycyl)amino]methyl-1-(4-chlorobenzyl)piperidine (Compd. No. 434)

[0234] A chloroform (0.4 mL) solution of benzoyl chloride (0.060 mmol) was added to a chloroform (1.0 mL) solution of 3-[(glycylamino)methyl]-1-(4-chlorobenzyl)piperidine (0.050 mmol) and triethylamine (0.070 mmol). The resulting reaction mixture was shaken at room temperature for 2.5 hours, and an (aminomethyl)polystyrene resin (1.04 mmol/g, 50 mg, 50 mmol) was then added to the obtained mixture. The resulting mixture was shaken at room temperature for 12 hours and filtered, and the resin was washed with dichloromethane (0.5 mL). The filtrate and washings were combined, and dichloromethane (4 mL) was added. The obtained mixture was washed with an 2 M aqueous solution of NaOH (0.5 mL) and concentrated to thereby afford 3-[(N-benzoylglycyl)amino]methyl-1-(4-chlorobenzyl)piperidine (Compd. No. 434) (14.7 mg, 74%). The purity was determined by RPLC/MS (91%). ESI/MS m/e 400 (M⁺+H, C₂₂H₂₆ClN₃O₂).

[Examples 1036 to 1058]

[0235] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1035. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 24.

Table 24

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1036	435	C ₂₆ H ₂₈ ClN ₃ O ₂	450	16.0	71
1037	436	C ₂₂ H ₂₅ ClN ₄ O ₄	445	18.9	85
1038	437	C ₂₄ H ₂₈ ClN ₃ O ₄	458	18.2	79
1039	438	C ₂₃ H ₂₅ ClF ₃ N ₃ O ₂	468	19.0	81
1040	439	C ₂₃ H ₂₄ ClF ₄ N ₃ O ₂	486	20.2	83
1041	440	C ₂₃ H ₂₅ ClF ₃ N ₃ O ₃	484	18.9	78
1042	441	C ₂₂ H ₂₅ BrClN ₃ O ₂	478	19.2	80
1043	442	C ₂₂ H ₂₅ Cl ₂ N ₃ O ₂	434	17.3	80
1044	443	C ₂₂ H ₂₅ BrClN ₃ O ₂	478	18.8	79
1045	444	C ₂₂ H ₂₄ ClF ₂ N ₃ O ₂	436	16.7	77
1046	445	C ₂₂ H ₂₄ Cl ₃ N ₃ O ₂	468	17.9	76

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Table 24 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1047	446	C ₂₃ H ₂₈ ClN ₃ O ₂	414	14.6	71
1048	447	C ₂₇ H ₃₀ ClN ₃ O ₂	464	17.0	73
1049	448	C ₂₃ H ₂₇ ClN ₄ O ₄	459	19.5	85
1050	449	C ₂₅ H ₃₀ ClN ₃ O ₄	472	17.1	72
1051	450	C ₂₄ H ₂₇ ClF ₃ N ₃ O ₂	482	19.4	81
1052	451	C ₂₄ H ₂₆ ClF ₄ N ₃ O ₂	500	18.2	73
1053	452	C ₂₄ H ₂₇ ClF ₃ N ₃ O ₃	498	18.8	76
1054	453	C ₂₃ H ₂₇ BrClN ₃ O ₂	492	19.4	79
1055	454	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₂	448	16.5	74
1056	455	C ₂₃ H ₂₇ BrClN ₃ O ₂	492	19.3	78
1057	456	C ₂₃ H ₂₆ ClF ₂ N ₃ O ₂	450	17.1	76
1058	457	C ₂₃ H ₂₆ Cl ₃ N ₃ O ₂	482	16.9	70

[Reference Example 18] Synthesis of 4-(aminomethyl)-1-(4-chlorobenzyl)piperidine

[0236] K₂CO₃ (3.02 g) and 4-chlorobenzyl chloride (3.52 g, 21.8 mmol) were successively added to an acetonitrile (100 mL) solution of 4-(aminomethyl)piperidine (7.00 g, 61.3 mmol). The resulting reaction mixture was stirred at 60 °C for 16 hours, cooled to 25 °C and concentrated. The obtained residue was fractionated between dichloromethane (75 mL) and water (50 mL) and then washed with water (50 mL×2) and brine (50 mL×1). The organic layer was dried (over MgSO₄), concentrated and then purified by chromatography (SiO₂, 4% H₂O-*i*PrOH) to provide 4-(aminomethyl)-1-(4-chlorobenzyl)piperidine (3.58 g, 69%).

[Example 1059] Synthesis of 4-[(N-benzoylglycyl)amino]methyl-1-(4-chlorobenzyl)piperidine (Compd. No. 458)

[0237] Hippuric acid (38 mg, 0.21 mmol), EDCI (48 mg, 0.24 mmol), HOBt (31 mg, 0.23 mmol) and triethylamine (38 μL, 0.27 mmol) were added to a dichloromethane (1 mL) solution of 4-(aminomethyl)-1-(4-chlorobenzyl)piperidine (50 mg, 0.21 mmol). The resulting reaction mixture was shaken at 25 °C for 16 hours, then diluted with 1 mL of dichloromethane, washed with a 2 M aqueous solution of NaOH (0.75 mL×2), dried (over MgSO₄), concentrated and purified by chromatography (SiO₂, 6-8% methanol/dichloromethane) to thereby afford 4-[(N-benzoylglycyl)amino]methyl-1-(4-chlorobenzyl)piperidine (Compd. No. 458). The resulting compound was treated with TFA to provide a TFA salt (105 mg, 97%). The purity was determined by RPLC/MS (85%). ESI/MS m/e 400 (M⁺+H, C₂₂H₂₆ClN₃O₂).

[Examples 1060 to 1086]

[0238] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1059. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 25.

Table 25

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1060	459	C ₂₃ H ₂₈ ClN ₃ O ₂	414	86*	78
1061	460	C ₂₃ H ₂₈ ClN ₃ O ₂	414	55	Q
1062	461	C ₂₃ H ₂₅ ClF ₃ N ₃ O ₂	468	65	Q
1063	462	C ₂₃ H ₂₈ ClN ₃ O ₂	414	61	Q

Notes: * indicates "yield (mg) of trifluoroacetate".
Q means "Quantitative".

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Table 25 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1064	463	C ₂₃ H ₂₈ ClN ₃ O ₂	414	54	Q
1065	464	C ₂₅ H ₃₂ ClN ₃ O ₅	490	56	Q
1066	465	C ₂₁ H ₂₅ ClN ₄ O ₂	401	38	96
1067	466	C ₂₂ H ₂₅ ClN ₄ O ₄	445	15	34
1068	557	C ₂₃ H ₂₈ ClN ₃ O ₂	414	58*	66
1069	558	C ₂₃ H ₂₈ ClN ₃ O ₂	414	55	Q
1070	618	C ₂₅ H ₃₂ ClN ₃ O ₂	442	58	Q
1071	686	C ₂₆ H ₃₄ ClN ₃ O ₂	456	62	Q
1072	749	C ₃₄ H ₃₇ ClN ₄ O ₂	569	7.2*	18
1073	750	C ₂₄ H ₃₀ ClN ₃ O ₃	444	4.7*	14
1074	840	C ₂₄ H ₂₉ ClN ₂ O ₂	413	52*	58
1075	841	C ₂₃ H ₂₇ ClN ₂ O ₂	399	52	Q
1076	842	C ₂₃ H ₂₆ Cl ₂ N ₂ O ₂	433	55	Q
1077	843	C ₂₅ H ₃₁ ClN ₂ O ₂	427	58	Q
1078	844	C ₂₄ H ₂₉ ClN ₂ O ₂	413	56	Q
1079	845	C ₂₄ H ₂₉ ClN ₂ O ₄ S	477	62	Q
1080	846	C ₂₉ H ₃₁ ClN ₂ O ₃	491	43	88
1081	847	C ₂₄ H ₂₈ ClFN ₂ O ₃	447	54	Q
1082	848	C ₂₅ H ₃₁ ClN ₂ O ₂	427	47	Q
1083	849	C ₂₅ H ₃₁ ClN ₂ O ₄	459	55	Q
1084	850	C ₂₂ H ₂₇ ClN ₂ O ₃ S	435	46	Q
1085	873	C ₂₀ H ₂₈ ClN ₃ O ₂	378	44.8	Q
1086	874	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₃	464	51	Q

Notes: * indicates "yield (mg) of trifluoroacetate".
Q means "Quantitative".

[Reference Example 19] Synthesis of 1-(4-chlorobenzyl)-4-[N-(3,3-diphenylpropyl)aminomethyl]piperidine

[0239] 4-(Aminomethyl)-1-(4-chlorobenzyl)piperidine (120 mg) was reacted with 3,3-diphenylpropyl methanesulfonate (1.0 equivalent) in the presence of NaI (2.6 equivalents) in acetonitrile at 70 °C for 16 hours. After treatment by a conventional method, the obtained crude product was purified by column chromatography (SiO₂) to afford 1-(4-chlorobenzyl)-4-[N-(3,3-diphenylpropyl)aminomethyl]piperidine (118 mg, 54%). The purity was determined by RPLC/MS (98%).

[Reference Example 20] Synthesis of 1-(4-chlorobenzyl)-4-[N-(2,2-diphenylethyl)aminomethyl]piperidine

[0240] 4-(Aminomethyl)-1-(4-chlorobenzyl)piperidine (120 mg) was subjected to reducing amination in methanol by using 2,2-diphenylacetaldehyde (0.66 equivalent) and a polymer-supported boron hydride at 25 °C for 16 hours and then subjected to treatment according to a conventional method and column chromatography (SiO₂) to thereby provide 1-(4-chlorobenzyl)-4-[N-(2,2-diphenylethyl)aminomethyl]piperidine (70 mg, 49%). The purity was determined by RPLC/MS (98%).

[Example 1087] Synthesis of 4-[N-(N-benzoylglycyl)-N-(2,2-diphenylethyl)aminomethyl]-1-(4-chlorobenzyl)piperidine (Compd. No. 524)

[0241] Hippuric acid (1.1 equivalents), HBTU (1.1 equivalents) and HOBt (1.1 equivalents) were added to a dichloromethane solution of 1-(4-chlorobenzyl)-4-[N-(2,2-diphenylethyl)aminomethyl]piperidine (0.084 mmol). The resulting reaction mixture was stirred at 40 °C for 24 hours. The obtained crude product was subjected to treatment according to a conventional method and preparative TLC (SiO₂) to thereby provide 4-[N-(N-benzoylglycyl)-N-(2,2-diphenylethyl)aminomethyl]-1-(4-chlorobenzyl)piperidine (Compd. No. 524) (8.5 mg, 17%). The purity was determined by RPLC/MS (98%). ESI/MS m/e 580 (M⁺+H, C₃₆H₃₈ClN₃O₂).

[Examples 1088 to 1090]

[0242] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1087. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 26.

Table 26

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1088	521	C ₃₈ H ₃₉ ClF ₃ N ₃ O ₂	662	5.5	10
1089	522	C ₃₇ H ₃₇ ClF ₃ N ₃ O ₂	648	8.6	16
1090	523	C ₃₇ H ₄₀ ClN ₃ O ₂	594	4.8	10

[Reference Example 21] Synthesis of 1-(4-chlorobenzyl)-4-[(valylamino)methyl]piperidine

[0243] Triethylamine (0.76 mL, 5.44 mmol), di-N-(tert-butoxycarbonyl)valine (1.09 g, 5.03 mmol), EDCI (883 mg, 4.61 mmol) and HOBt (623 mg, 4.61 mmol) were added to a dichloromethane (21 mL) solution of 4-(aminomethyl)-1-(4-chlorobenzyl)piperidine (1.0 g, 4.2 mmol). The resulting reaction mixture was stirred at 25 °C for 16 hours, then diluted with dichloromethane (20 mL), washed with a 2 M aqueous solution of NaOH (20 mL×2) and brine (20 mL×1), dried (over MgSO₄) and concentrated. The obtained crude product was purified by chromatography (SiO₂, 3% methanol/dichloromethane) to thereby afford 1-(4-chlorobenzyl)-4-[(N-Boc-valyl)amino]methyl]piperidine (1.1 g, 60%) as a light amber oil. ESI/MS m/e 438 (M⁺+H).

[0244] 1-(4-Chlorobenzyl)-4-[(N-Boc-valyl)amino]methyl]piperidine (1.1 g, 2.51 mmol) was dissolved in a 3 M HCl-methanol solution (25 mL) and stirred at 25 °C for 1 hour. The resulting reaction mixture was concentrated, and the obtained salt was dissolved in ^tBuOH/H₂O =3:1 (25 mL). An anion (OH⁻) exchange resin was added until the solution became slightly basic. The obtained mixture was filtered and concentrated to provide 1-(4-chlorobenzyl)-4-[(valylamino)methyl]piperidine (819 mg, 97%). Further purification was not required for the resulting compound. ESI/MS m/e 338.1 (M⁺+H, C₁₈H₂₈ClN₃O).

[0245] Other 4-[(acylamino)methyl]-1-(4-chlorobenzyl)piperidines were synthesized by using the respective corresponding starting materials and reactants according to the method of Reference Example 21.

[0246] 1-(4-chlorobenzyl)-4-[(glycylamino)methyl]piperidine: 0.830g, 67% (two steps), ESI/MS 269 (M⁺+H).

[0247] 1-(4-chlorobenzyl)-4-[(serylamino)methyl]piperidine: 0.286 g, 20% (two steps), ESI/MS 326 (M⁺+H).

[0248] 4-[(alanylamino)methyl]-1-(4-chlorobenzyl)piperidine: 1.20g, 65% (two steps), ESI/MS 310 (M⁺+H).

[0249] 1-(4-chlorobenzyl)-4-[(prolylamino)methyl]piperidine: 1.48g, 86% (two steps), ESI/MS 336 (M⁺+H).

[0250] 1-(4-chlorobenzyl)-4-[(glutaminylamino)methyl]piperidine: 0.830g, 27% (two steps), ESI/MS 367 (M⁺+H).

[0251] 1-(4-chlorobenzyl)-4-[(2-methylalanyl)amino]methyl]piperidine: 2.24 g, 62% (two steps), ESI/MS 324 (M⁺+H).

[0252] 1-(4-chlorobenzyl)-4-[(O-methylseryl)amino]methyl]piperidine: 0.686 g, 38% (two steps), ESI/MS 340 (M⁺+H).

[0253] 1-(4-chlorobenzyl)-4-[(1-aminocyclopropylcarbonyl)amino]methyl]piperidine: 2.03g, 82% (two steps), ESI/MS 322 (M⁺+H).

[0254] 1-(4-chlorobenzyl)-4-[(leucylamino)methyl]piperidine: 1.30 g, 58% (two steps), ESI/MS 352 (M⁺+H).

[0255] 1-(4-chlorobenzyl)-4-[(O-benzylseryl)amino]methyl]piperidine: 1.34 g, 56% (two steps), ESI/MS 416 (M⁺+H).

[Reference Example 22] Synthesis of 1-(tert-butoxycarbonyl)-4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]piperidine

[0256] Triethylamine (3.51 g), N-(9-fluorenylmethyloxycarbonyl)glycine (7.93 g, 26.7 mmol), EDCI (3.80 g) and HOBt (4.33 g) were added to a dichloromethane (150 mL) solution of 4-(aminomethyl)-1-(tert-butoxycarbonyl)piperidine (5.72 g). The resulting reaction mixture was stirred at room temperature for 18 hours, then washed with water (100 mL×3) and brine (100 mL×2), dried over anhydrous sodium sulfate, concentrated and recrystallized from acetonitrile/methanol (150 mL/1 mL) at 0 °C to provide 1-(tert-butoxycarbonyl)-4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]piperidine (5.75 g, 44%) as an off-white crystal.

[Reference Example 23] Synthesis of 4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]piperidine

[0257] 1-(tert-Butoxycarbonyl)-4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]piperidine (3.17 g, 6.42 mmol) was added to a 4 M dioxane solution of HCl. The resulting solution was stirred at room temperature for 5 hours and concentrated to afford 4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]piperidine (3.85 g) as an off-white solid. The obtained product was used without further purification.

[Reference Example 24] Synthesis of 4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]-1-(4-methylthiobenzyl)piperidine

[0258] 4-Methylthiobenzaldehyde (1.24 g) and NaBH(OAc)₃ (2.56 g) were added to a 1% acetic acid/DMF (15 mL) solution of 4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]piperidine (1.00 g, 2.33 mmol). The resulting reaction mixture was stirred at 60 °C for 1 hour, cooled to room temperature and concentrated. A saturated aqueous solution (50 mL) of NaHCO₃ was added to the resultant residue, and the obtained mixture was extracted with ethyl acetate (50 mL×2). The extracts were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude product was purified by column chromatography (SiO₂, 50%-10% methanol-dichloromethane) to thereby afford 4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]-1-(4-methylthiobenzyl)piperidine (602 mg) as a colorless oil.

[Reference Example 25] Synthesis of 1-(4-ethylbenzyl)-4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]piperidine

[0259] 4-Ethylbenzaldehyde (1.09 g, 8.16 mmol) and NaBH₃CN (6.59 g, 10.5 mmol) were added to a 2.5% acetic acid/methanol (80 mL) solution of 4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]piperidine (1.00 g, 2.33 mmol). The resulting reaction mixture was stirred at 60 °C for 13 hours and cooled to room temperature. A 1 M aqueous solution of NaOH (50 mL) and dichloromethane (50 mL) were then added, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (50 mL×3). The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography (SiO₂, methanol/ethyl acetate = 2:8) to thereby provide 1-(4-ethylbenzyl)-4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]piperidine (740 mg, 62%).

[Reference Example 26] Synthesis of 4-[(glycylamino)methyl]-1-(4-methylthiobenzyl)piperidine

[0260] A DMF (4 mL) solution of 4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]-1-(4-methylthiobenzyl)piperidine (590 mg) and piperidine (1 mL) was stirred at 60 °C for 2 hours. After concentrating, the obtained crude product was purified by column chromatography (SiO₂, triethylamine/methanol/dichloromethane = 1:1:9) to thereby afford 4-[(glycylamino)methyl]-1-(4-methylthiobenzyl)piperidine (365 mg) as a white solid. ¹H NMR (CDCl₃, 270MHz) δ 1.25 (dd, J = 12 Hz, 4.1 Hz, 2H), 1.34 (dd, J = 12 Hz, 4.1 Hz, 2H), 1.51 (br-s, 2H), 1.66 (d, J = 12 Hz, 2H), 1.77 (d, J = 7.3 Hz, 1H), 1.94 (t, J = 9.5 Hz, 2H), 2.48 (s, 3H), 2.80 (d, J = 12 Hz, 2H), 3.18 (t, J = 6.2 Hz, 2H), 3.35 (s, 2H), 3.45 (s, 2H), 7.18-7.29 (m, 4H), 7.35 (br-s, 1H).

[0261] Further, 1-(4-ethylbenzyl)-4-[(glycylamino)methyl]piperidine was synthesized by using the corresponding starting material and reactants according to the method of Reference Example 26: 333 mg, 79%.

[Reference Example 27] Synthesis of 4-[(glycylamino)methyl]-1-(4-fluorobenzyl)piperidine

[0262] An acetonitrile (200 mL) solution of 4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]piperidine (1.50 g, 3.49 mmol), 4-fluorobenzyl bromide (0.478 mL, 3.84 mmol) and triethylamine (1.47 mL, 10.5 mmol) was stirred at room temperature for 13 hours. The obtained product was purified by column chromatography (SiO₂, 10% methanol/dichloromethane) to thereby provide 4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]piperidine. A DMF (5

mL) solution of the 4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]piperidine and piperidine (5 mL) was further stirred at room temperature for 17 hours. After concentrating, the obtained crude product was purified by column chromatography (SiO₂, triethylamine/methanol/dichloromethane = 0.5:2:8) to afford 4-[(glycylamino)methyl]-1-(4-fluorobenzyl)piperidine (453 mg, 46%).

[Reference Example 28] Synthesis of 4-[(glycylamino)methyl]-1-[4-(N-phenylcarbamoyl)benzyl]piperidine

[0263] An acetonitrile (100 mL) solution of 4-(N-phenylcarbamoyl)benzyl chloride (800 mg, 3.26 mmol) was dropped into a mixture of 4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]piperidine (1.27 g, 2.96 mmol) with triethylamine (1.25 mL, 8.88 mmol), KI (50 mg, 0.30 mmol) and acetonitrile (200 mL). The resulting mixture was stirred at room temperature for 19 hours and stirred at 60 °C for another 5 hours. After concentrating, the obtained crude product was purified by column chromatography (SiO₂, 5% methanol/dichloromethane-triethylamine/methanol/dichloromethane = 2:2:96) to provide 4-[(glycylamino)methyl]-1-[4-(N-phenylcarbamoyl)benzyl]piperidine (340 mg, 30%).

[Example 1091] Synthesis of 1-(4-chlorobenzyl)-4-[[N-(3-cyanobenzoyl)valyl]aminomethyl]piperidine (Compd. No. 619)

[0264] Triethylamine (0.011 mL, 0.077 mmol), m-cyanobenzoic acid (28 mg, 0.071 mmol), EDCI (13 mg, 0.065 mmol) and HOBT (9 mg, 0.065 mmol) were added to a dichloromethane (0.60 mL) solution of 1-(4-chlorobenzyl)-4-[(valylamino)methyl]piperidine (20 mg, 0.059 mmol). The resulting reaction mixture was stirred at 25 °C for 16 hours, and the obtained solution was diluted with dichloromethane (0.75 mL), washed with a 2 M aqueous solution of NaOH (0.75 mL×2) and dried by filtration through a PTFE membrane. The dried solution was concentrated to thereby afford 1-(4-chlorobenzyl)-4-[[N-(3-cyanobenzoyl)valyl]aminomethyl]piperidine (Compd. No. 619) (24.2 mg, 88%). Further purification was not required for the resulting compound. The purity was determined by RPLC/MS (85%). ESI/MS m/e 467 (M⁺+H, C₂₆H₃₁ClN₄O₂).

[Examples 1092 to 1543]

[0265] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1091. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 27.

Table 27

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1092	467	C ₂₂ H ₂₅ BrClN ₃ O ₂	478	11	46
1093	468	C ₂₄ H ₃₁ ClN ₄ O ₂	443	9	41
1094	469	C ₂₃ H ₂₈ ClN ₃ O ₃	430	7*	27
1095	470	C ₂₃ H ₂₅ ClN ₄ O ₂	425	21	Q
1096	471	C ₂₄ H ₂₈ ClN ₃ O ₄	458	7	29
1097	472	C ₂₉ H ₃₁ N ₃ O ₃	504	5*	21
1098	473	C ₂₄ H ₂₈ ClN ₃ O ₃	442	16	71
1099	474	C ₂₃ H ₂₅ ClF ₃ N ₃ O ₂	468	14	60
1100	475	C ₂₅ H ₃₂ ClN ₃ O ₂	442	5	22
1101	476	C ₂₂ H ₂₅ ClN ₄ O ₄	445	4	17
1102	477	C ₂₅ H ₃₂ ClN ₃ O ₃	458	10*	36
1103	478	C ₂₁ H ₂₇ ClN ₄ O ₂	403	9	47
1104	479	C ₂₀ H ₂₄ ClN ₃ O ₃	390	17	87
1105	480	C ₂₀ H ₂₃ BrClN ₃ O ₃	470	23	Q

Notes: * indicates "yield (mg) of trifluoroacetate".

Q means "Quantitative".

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Table 27 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	1106	C ₂₀ H ₂₄ ClN ₃ O ₂ S	406	7	33
	1107	C ₂₁ H ₂₆ ClN ₃ O ₂ S	420	9	45
	1108	C ₂₁ H ₂₆ ClN ₃ O ₂ S	420	8	40
10	1109	C ₂₄ H ₂₇ ClN ₄ O ₂	439	9*	34
	1110	C ₂₄ H ₂₄ ClF ₆ N ₃ O ₂	536	13	49
	1111	C ₂₃ H ₂₅ ClN ₄ O ₂	425	16	74
15	1112	C ₂₂ H ₂₅ Cl ₂ N ₃ O ₂	434	5	24
	1113	C ₂₂ H ₂₇ ClN ₄ O ₂	415	7	32
	1114	C ₂₄ H ₂₄ ClF ₆ N ₃ O ₂	536	21	78
20	1115	C ₂₄ H ₃₀ ClN ₃ O ₃	444	8	35
	1116	C ₂₃ H ₂₄ ClF ₄ N ₃ O ₂	486	19	79
	1117	C ₂₃ H ₂₅ ClF ₃ N ₃ O ₃	484	18	76
25	1118	C ₂₃ H ₂₄ Cl ₂ F ₃ N ₃ O ₂	502	23	92
	1119	C ₂₃ H ₂₄ ClF ₄ N ₃ O ₂	486	19	79
	1120	C ₂₃ H ₂₄ ClF ₄ N ₃ O ₂	486	20	83
30	1121	C ₂₃ H ₂₄ ClF ₄ N ₃ O ₂	486	12	48
	1122	C ₂₅ H ₃₂ ClN ₃ O ₃	458	4	16
	1123	C ₂₃ H ₂₆ ClF ₃ N ₄ O ₂	483	13	52
35	1124	C ₂₄ H ₃₁ ClN ₄ O ₂	443	8	36
	1125	C ₂₃ H ₂₈ ClN ₃ O ₃	430	10	48
	1126	C ₂₂ H ₂₄ BrClN ₄ O ₄	523	10	39
40	1127	C ₂₂ H ₂₄ ClFN ₄ O ₄	463	4	17
	1128	C ₂₂ H ₂₄ Cl ₂ N ₄ O ₄	479	12	52
	1129	C ₂₄ H ₃₀ ClN ₃ O ₄	460	11	43
45	1130	C ₂₂ H ₂₄ BrClN ₄ O ₄	523	2	8
	1131	C ₂₀ H ₂₃ ClN ₄ O ₅	435	2	10
	1132	C ₂₁ H ₂₆ ClN ₃ O ₃	404	9	44
50	1133	C ₂₄ H ₂₆ ClN ₃ O ₂ S	456	1	5
	1134	C ₂₀ H ₂₃ BrClN ₃ O ₂ S	484	12	48
	1135	C ₂₂ H ₂₈ ClN ₃ O ₃	418	9	44
55	1136	C ₂₄ H ₃₂ ClN ₃ O ₃	446	9	40
	1137	C ₂₅ H ₂₉ ClN ₄ O ₂	453	10	45
	1138	C ₂₄ H ₂₈ ClN ₃ O ₃	442	9	41
	1139	C ₂₆ H ₃₄ ClN ₃ O ₂	456	11	49
	1140	C ₂₃ H ₂₈ ClN ₃ O ₃	430	5	24
	1141	C ₂₃ H ₂₈ ClN ₃ O ₄ S	478	20	85

Notes: * indicates "yield (mg) of trifluoroacetate".

Q means "Quantitative".

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Table 27 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	1142	C ₂₀ H ₂₄ ClN ₃ O ₃	390	6	31
	1143	C ₂₀ H ₂₄ ClN ₃ O ₂ S	406	8	39
	1144	C ₂₅ H ₃₀ ClF ₃ N ₄ O ₄	543	28.2	95
10	1145	C ₂₀ H ₂₃ ClN ₄ O ₄ S	451	9	39
	1146	C ₃₁ H ₃₃ ClN ₄ O ₂	529	5	17
	1147	C ₂₁ H ₂₆ ClN ₃ O ₃ S	436	8	37
15	1148	C ₂₂ H ₂₈ ClN ₃ O ₃	418	8	40
	1149	C ₂₁ H ₂₆ ClN ₃ O ₃	404	6	32
	1150	C ₂₁ H ₂₅ ClN ₄ O ₅	449	5	20
20	1151	C ₂₂ H ₂₆ ClN ₃ O ₃ S	448	8	37
	1152	C ₂₃ H ₃₁ ClN ₄ O ₂	431	6	28
	1153	C ₂₅ H ₃₄ ClN ₃ O ₃	460	8	34
25	1154	C ₂₇ H ₃₀ ClN ₃ O ₃	480	9	36
	1155	C ₂₂ H ₂₅ ClF ₃ N ₃ O ₃	472	18	75
	1156	C ₂₅ H ₂₉ ClN ₄ O ₂	453	8	36
30	1157	C ₂₂ H ₂₆ ClN ₅ O ₄	460	2.4	10
	1158	C ₂₄ H ₃₀ ClN ₃ O ₂	428	4.6*	51
	1159	C ₂₄ H ₃₀ ClN ₃ O ₂	428	20.6*	71
35	1160	C ₂₂ H ₂₅ ClFN ₃ O ₂	418	15.8*	56
	1161	C ₂₂ H ₂₄ Cl ₃ N ₃ O ₂	468	7.3*	23
	1162	C ₂₂ H ₂₄ Cl ₃ N ₃ O ₂	468	17.4*	55
40	1163	C ₂₂ H ₂₄ Cl ₃ N ₃ O ₂	468	14.1*	44
	1164	C ₂₂ H ₂₄ Cl ₃ N ₃ O ₂	468	6.8*	22
	1165	C ₂₂ H ₂₄ Cl ₂ N ₄ O ₄	479	5.7*	18
45	1166	C ₂₂ H ₂₄ Cl ₂ N ₄ O ₄	479	18.9*	58
	1167	C ₂₄ H ₃₀ ClN ₃ O ₂	428	14.2*	49
	1168	C ₂₄ H ₂₇ ClF ₃ N ₃ O ₂	482	30.6*	94
50	1169	C ₂₅ H ₂₆ ClF ₆ N ₃ O ₂	550	38.0*	Q
	1170	C ₂₄ H ₂₆ ClFN ₄ O ₂	457	0.9*	3
	1171	C ₂₄ H ₂₆ Cl ₂ N ₄ O ₂	473	11.1*	35
55	1172	C ₂₅ H ₂₉ ClN ₄ O ₂	453	12.5*	41
	1173	C ₂₅ H ₂₆ ClF ₆ N ₃ O ₂	550	15	72
	1174	C ₂₄ H ₂₇ ClN ₄ O ₂	439	12	68
	1175	C ₂₃ H ₂₇ BrClN ₃ O ₂	494	14	73
	1176	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₂	448	13	75
	1177	C ₂₅ H ₂₆ ClF ₆ N ₃ O ₂	550	14	66

Notes: * indicates "yield (mg) of trifluoroacetate".
Q means "Quantitative".

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Table 27 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	1178	C ₂₅ H ₃₂ ClN ₃ O ₃	458	5	28
	1179	C ₂₄ H ₂₆ ClF ₄ N ₃ O ₂	500	12	61
	1180	C ₂₄ H ₂₇ ClF ₃ N ₃ O ₃	498	12	62
10	1181	C ₂₄ H ₂₆ Cl ₂ F ₃ N ₃ O ₂	516	12	61
	1182	C ₂₄ H ₂₆ ClF ₄ N ₃ O ₂	500	15	77
	1183	C ₂₄ H ₂₆ ClF ₄ N ₃ O ₂	500	11	59
15	1184	C ₂₄ H ₂₆ ClF ₄ N ₃ O ₂	500	16	84
	1185	C ₂₆ H ₃₄ ClN ₃ O ₃	472	14	77
	1186	C ₂₄ H ₂₈ ClF ₃ N ₄ O ₂	497	11	55
20	1187	C ₂₁ H ₂₅ BrClN ₃ O ₂ S	500	12	64
	1188	C ₂₁ H ₂₅ BrClN ₃ O ₂ S	500	15	75
	1189	C ₂₅ H ₃₄ ClN ₃ O ₃	460	16	87
25	1190	C ₂₂ H ₂₈ ClN ₃ O ₂ S ₂	466	13	71
	1191	C ₂₂ H ₂₈ ClN ₃ O ₃	418	12	72
	1192	C ₂₅ H ₂₈ ClN ₃ O ₂ S	470	15	81
30	1193	C ₂₅ H ₂₉ ClN ₄ O ₂	453	17	94
	1194	C ₂₂ H ₂₈ ClN ₃ O ₂ S	434	15	91
	1195	C ₂₁ H ₂₆ ClN ₃ O ₂ S	420	13	80
35	1196	C ₂₂ H ₂₈ ClN ₃ O ₂ S	434	10	59
	1197	C ₂₆ H ₃₁ ClN ₄ O ₂	467	6	31
	1198	C ₃₀ H ₃₂ ClN ₃ O ₃	518	18	92
40	1199	C ₂₄ H ₂₇ ClN ₄ O ₂	439	14	85
	1200	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₂	448	17	97
	1201	C ₂₄ H ₂₇ ClF ₃ N ₃ O ₂	482	17	91
45	1202	C ₂₃ H ₂₉ ClN ₄ O ₂	429	5	29
	1203	C ₂₇ H ₃₆ ClN ₃ O ₂	470	4	24
	1204	C ₂₆ H ₃₄ ClN ₃ O ₂	456	6	36
50	1205	C ₂₅ H ₃₃ ClN ₄ O ₂	457	7	38
	1206	C ₂₄ H ₃₀ ClN ₃ O ₃	444	4	20
	1207	C ₂₄ H ₃₀ ClN ₃ O ₃	444	2	14
55	1208	C ₂₃ H ₂₈ ClN ₃ O ₃	430	4	25
	1209	C ₂₅ H ₃₀ ClN ₃ O ₄	472	7	38
	1210	C ₂₅ H ₃₀ ClN ₃ O ₃	456	7	40
	1211	C ₂₅ H ₃₀ ClN ₃ O ₃	456	15	85
	1212	C ₂₁ H ₂₆ ClN ₃ O ₃	404	15	94
	1213	C ₂₂ H ₂₉ ClN ₄ O ₂	417	5	30
	1214	C ₂₁ H ₂₅ BrClN ₃ O ₃	484	6	34
	1215	C ₂₄ H ₃₀ ClN ₃ O ₃	444	5	28

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Table 27 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	1216	C ₂₅ H ₃₃ ClN ₄ O ₂	457	5	28
	1217	C ₂₃ H ₂₉ ClN ₄ O ₂	429	4	22
	1218	C ₂₁ H ₂₇ ClN ₄ O ₂	403	9	58
10	1219	C ₂₁ H ₂₆ ClN ₃ O ₃	404	17	87
	1220	C ₂₁ H ₂₆ ClN ₃ O ₂ S	420	15	74
	1221	C ₂₂ H ₂₈ ClN ₃ O ₃ S	450	31	Q
15	1222	C ₂₃ H ₃₀ ClN ₃ O ₃	432	17	80
	1223	C ₂₂ H ₂₈ ClN ₃ O ₃	418	18	89
	1224	C ₂₃ H ₂₈ ClN ₃ O ₃ S	462	20	86
20	1225	C ₂₆ H ₃₆ ClN ₃ O ₃	474	21	90
	1226	C ₂₈ H ₃₂ ClN ₃ O ₃	494	20	84
	1227	C ₂₃ H ₂₇ ClF ₃ N ₃ O ₃	486	19	81
25	1228	C ₂₄ H ₃₃ ClN ₄ O ₂	445	23	Q
	1229	C ₂₅ H ₂₉ ClN ₄ O ₂	453	4	20
	1230	C ₃₂ H ₃₅ ClN ₄ O ₂	543	11	40
30	1231	C ₂₅ H ₂₇ ClF ₃ N ₃ O ₂	482	6.7	37
	1232	C ₂₅ H ₃₁ BrClN ₃ O ₂	520	15	49
	1233	C ₂₅ H ₃₁ Cl ₂ N ₃ O ₂	476	18	64
35	1234	C ₂₇ H ₃₇ ClN ₄ O ₂	485	14	50
	1235	C ₂₆ H ₃₄ ClN ₃ O ₃	472	19	69
	1236	C ₂₅ H ₃₁ ClN ₄ O ₄	487	21	73
40	1237	C ₂₅ H ₃₃ ClN ₄ O ₂	457	19	69
	1238	C ₂₇ H ₃₀ ClF ₆ N ₃ O ₂	578	8	25
	1239	C ₂₇ H ₃₆ ClN ₃ O ₃	486	16	55
45	1240	C ₂₇ H ₃₄ ClN ₃ O ₄	500	24	80
	1241	C ₂₆ H ₃₀ ClF ₄ N ₃ O ₂	528	18	56
	1242	C ₂₆ H ₃₁ ClF ₃ N ₃ O ₃	526	21	68
50	1243	C ₂₆ H ₃₀ Cl ₂ F ₃ N ₃ O ₂	544	15	48
	1244	C ₂₆ H ₃₀ ClF ₄ N ₃ O ₂	528	13	41
	1245	C ₂₆ H ₃₀ ClF ₄ N ₃ O ₂	528	20	63
55	1246	C ₂₆ H ₃₀ ClF ₄ N ₃ O ₂	528	19	62
	1247	C ₂₈ H ₃₈ ClN ₃ O ₃	500	11	36
	1248	C ₂₆ H ₃₄ ClN ₃ O ₂	456	21	89
55	1249	C ₂₆ H ₃₁ ClF ₃ N ₃ O ₂	510	20	95
	1250	C ₂₆ H ₃₁ ClN ₄ O ₂	467	15	54
	1251	C ₂₇ H ₃₇ ClN ₄ O ₂	485	19	66
55	1252	C ₂₆ H ₃₄ ClN ₃ O ₃	472	16	56
	1253	C ₂₇ H ₃₄ ClN ₃ O ₄	500	18	59

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Table 27 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	1254	C ₃₂ H ₃₆ ClN ₃ O ₃	546	24	73
	1255	C ₂₆ H ₃₁ ClF ₃ N ₃ O ₂	510	16	54
	1256	C ₂₉ H ₄₀ ClN ₃ O ₂	498	18	61
10	1257	C ₂₅ H ₂₃ ClN ₄ O ₂	457	22	78
	1258	C ₂₆ H ₃₄ ClN ₃ O ₃	472	13	47
	1259	C ₂₇ H ₃₄ ClN ₃ O ₃	500	13	46
15	1260	C ₂₈ H ₃₈ ClN ₃ O ₂	484	17	60
	1261	C ₂₈ H ₃₈ ClN ₃ O ₃	500	12.5	42
	1262	C ₃₂ H ₃₆ ClN ₃ O ₃	546	1*	2
20	1263	C ₂₈ H ₃₅ ClN ₄ O ₂	495	4*	12
	1264	C ₂₅ H ₃₁ ClN ₄ O ₄	487	5*	14
	1265	C ₃₀ H ₄₂ ClN ₃ O ₃	528	1*	3
25	1266	C ₂₇ H ₃₄ ClN ₃ O ₃	484	7*	21
	1267	C ₂₆ H ₃₂ ClF ₃ N ₄ O ₂	525	6*	16
	1268	C ₂₃ H ₃₀ ClN ₃ O ₃	432	6*	18
30	1269	C ₂₃ H ₃₀ ClN ₃ O ₂ S	448	4*	13
	1270	C ₂₇ H ₃₃ ClN ₄ O ₂	48	1*	4
	1271	C ₂₃ H ₂₉ ClN ₄ O ₄ S	493	4*	10
35	1272	C ₃₄ H ₃₉ ClN ₄ O ₂	571	3*	7
	1273	C ₂₄ H ₃₂ ClN ₃ O ₃ S	478	3*	7
	1274	C ₂₅ H ₃₄ ClN ₃ O ₃	460	2*	6
40	1275	C ₂₄ H ₃₂ ClN ₃ O ₃	446	2*	5
	1276	C ₂₄ H ₃₁ ClN ₄ O ₅	491	2*	5
	1277	C ₂₅ H ₃₂ ClN ₃ O ₃ S	490	1*	3
45	1278	C ₂₆ H ₃₇ ClN ₄ O ₂	473	3*	7
	1279	C ₃₀ H ₃₆ ClN ₃ O ₃	522	3*	7
	1280	C ₂₅ H ₃₁ ClF ₃ N ₃ O ₃	514	2*	6
50	1281	C ₂₄ H ₃₃ ClN ₄ O ₂	445	15*	45
	1282	C ₂₃ H ₂₉ BrClN ₃ O ₃	510	3*	7
	1283	C ₂₃ H ₂₉ ClN ₄ O ₅	477	2*	5
55	1284	C ₂₃ H ₃₁ ClN ₄ O ₂	431	2*	7
	1285	C ₂₃ H ₃₀ ClN ₃ O ₂ S	448	2*	6
	1286	C ₂₄ H ₃₂ ClN ₃ O ₂ S	462	3*	9
	1287	C ₂₄ H ₃₂ ClN ₃ O ₂ S	462	1*	4
	1288	C ₂₇ H ₃₃ ClN ₄ O ₂	482	2*	6
	1289	C ₂₈ H ₃₅ ClN ₄ O ₂	495	2*	6

Notes: * indicates "yield (mg) of trifluoroacetate".
Q means "Quantitative".

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Table 27 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	1290	C ₂₄ H ₃₂ CIN ₃ O ₃	446	3*	9
	1291	C ₂₇ H ₃₂ CIN ₃ O ₂ S	498	1*	3
	1292	C ₂₃ H ₂₉ BrCIN ₃ O ₂ S	526	2*	6
10	1293	C ₂₅ H ₃₄ CIN ₃ O ₃	460	2*	5
	1294	C ₂₇ H ₃₈ CIN ₃ O ₃	488	2*	4
	1295	C ₂₄ H ₃₂ CIN ₃ O ₂ S ₂	494	1*	4
15	1296	C ₂₆ H ₃₆ CIN ₃ O ₄ S ₂	554	2*	5
	1297	C ₂₄ H ₃₂ CIN ₃ O ₄ S ₂	526	3*	7
	1298	C ₂₅ H ₃₀ CIN ₃ O ₂	440	24	Q
20	1299	C ₂₇ H ₂₈ ClF ₆ N ₃ O ₂	576	28	98
	1300	C ₂₆ H ₂₉ CIN ₄ O ₂	465	23	99
	1301	C ₂₅ H ₂₉ BrCIN ₃ O ₂	518	26	99
25	1302	C ₂₇ H ₃₅ CIN ₄ O ₂	483	24	97
	1303	C ₂₆ H ₃₂ CIN ₃ O ₃	470	24	Q
	1304	C ₂₁ H ₂₈ ClF ₆ N ₃ O ₂	576	16	55
30	1305	C ₂₇ H ₃₄ CIN ₃ O ₃	484	25	Q
	1306	C ₂₇ H ₃₂ CIN ₃ O ₄	498	12	47
	1307	C ₂₆ H ₂₉ ClF ₃ N ₃ O ₃	524	25	95
35	1308	C ₂₆ H ₂₉ CIN ₄ O ₂	465	15	64
	1309	C ₂₇ H ₃₅ CIN ₄ O ₂	483	24	Q
	1310	C ₂₆ H ₃₂ CIN ₃ O ₃	470	26	Q
40	1311	C ₂₇ H ₃₂ CIN ₃ O ₄	498	15	62
	1312	C ₂₇ H ₃₂ CIN ₃ O ₃	482	11	44
	1313	C ₂₆ H ₂₉ ClF ₃ N ₃ O ₂	508	23	94
45	1314	C ₂₈ H ₃₆ CIN ₃ O ₂	482	26	Q
	1315	C ₂₅ H ₂₉ CIN ₄ O ₄	485	11	43
	1316	C ₂₄ H ₃₀ CIN ₃ O ₂ S	460	25	Q
50	1317	C ₂₄ H ₃₀ CIN ₃ O ₂ S	460	25	Q
	1318	C ₂₆ H ₂₉ ClF ₃ N ₃ O ₂	508	15	55
	1319	C ₂₃ H ₂₇ BrCIN ₃ O ₂ S	526	25	92
55	1320	C ₂₄ H ₃₀ CIN ₃ O ₂ S ₂	492	26	Q
	1321	C ₂₃ H ₂₇ BrCIN ₃ O ₂ S	526	25	94
	1322	C ₂₅ H ₃₂ CIN ₃ O ₃	458	26	Q
	1323	C ₂₇ H ₃₀ CIN ₃ O ₂ S	496	26	Q
	1324	C ₂₄ H ₃₀ CIN ₃ O ₃	444	26	Q
	1325	C ₂₈ H ₃₃ CIN ₄ O ₂	493	12	50

Notes: * indicates "yield (mg) of trifluoroacetate".
Q means "Quantitative".

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Table 27 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	1326	C ₂₃ H ₂₈ ClN ₃ O ₂ S	446	24	Q
	1327	C ₂₇ H ₃₁ ClN ₄ O ₂	479	32	Q
	1328	C ₂₃ H ₂₇ ClN ₄ O ₅	475	23	95
10	1329	C ₂₃ H ₂₉ ClN ₄ O ₂	429	24	Q
	1330	C ₂₃ H ₂₈ ClN ₃ O ₃	430	24	Q
	1331	C ₂₃ H ₂₇ BrClN ₃ O ₃	510	24	95
15	1332	C ₂₄ H ₃₁ ClN ₄ O ₂	443	22	98
	1333	C ₂₆ H ₃₂ ClN ₃ O ₃	470	9	37
	1334	C ₂₅ H ₃₁ ClN ₄ O ₂	455	10	44
20	1335	C ₂₉ H ₃₈ ClN ₃ O ₂	496	28	Q
	1336	C ₃₂ H ₃₄ ClN ₃ O ₃	544	26	95
	1337	C ₂₇ H ₃₃ ClN ₄ O ₃	497	3	11
25	1338	C ₂₅ H ₂₉ Cl ₂ N ₃ O ₂	474	25	Q
	1339	C ₂₅ H ₃₁ ClN ₄ O ₂	455	21	92
	1340	C ₂₅ H ₂₉ ClN ₄ O ₄	485	26	Q
30	1341	C ₂₅ H ₂₉ Cl ₂ N ₃ O ₂	474	21	90
	1342	C ₂₇ H ₃₂ ClN ₃ O ₃	482	10	41
	1343	C ₂₆ H ₂₈ ClF ₄ N ₃ O ₂	526	27	Q
35	1344	C ₂₈ H ₃₆ ClN ₃ O ₃	498	22	89
	1345	C ₂₆ H ₂₈ ClF ₄ N ₃ O ₂	526	25	94
	1346	C ₂₆ H ₂₈ ClF ₄ N ₃ O ₂	526	23	87
40	1347	C ₂₆ H ₃₀ ClF ₃ N ₄ O ₂	523	24	78
	1348	C ₂₆ H ₂₈ ClF ₄ N ₃ O ₂	526	21	66
	1349	C ₂₅ H ₃₂ ClN ₃ O ₃	458	23	84
45	1350	C ₂₇ H ₃₁ ClN ₄ O ₂	479	19	66
	1351	C ₂₄ H ₃₁ ClN ₄ O ₅	489	23	77
	1352	C ₂₃ H ₂₇ ClN ₄ O ₄ S	491	26	88
50	1353	C ₂₄ H ₃₀ ClN ₃ O ₃ S	476	23	82
	1354	C ₂₃ H ₂₈ ClN ₃ O ₃	430	21	81
	1355	C ₂₆ H ₃₂ ClN ₃ O ₂	454	25	91
55	1356	C ₂₇ H ₃₆ ClN ₃ O ₃	486	23	80
	1357	C ₂₆ H ₃₅ ClN ₄ O ₂	471	27	96
	1358	C ₂₅ H ₂₉ ClF ₃ N ₃ O ₃	512	23	74
55	1359	C ₂₃ H ₂₈ ClN ₃ O ₂ S	446	22	82
	1360	C ₂₄ H ₃₀ ClN ₃ O ₃	444	3	11
	1361	C ₂₅ H ₂₆ ClF ₆ N ₃ O ₃	566	7	20
55	1362	C ₂₄ H ₂₇ ClN ₄ O ₃	455	6	22
	1363	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₃	464	8	29

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Table 27 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	1364	C ₂₄ H ₃₀ CIN ₃ O ₄	460	6	22
	1365	C ₂₃ H ₂₇ CIN ₄ O ₅	475	5	18
	1366	C ₂₅ H ₃₂ CIN ₃ O ₄	474	5	18
10	1367	C ₂₅ H ₃₀ CIN ₃ O ₅	488	5	18
	1368	C ₂₄ H ₂₇ ClF ₃ N ₃ O ₄	514	6	20
	1369	C ₂₄ H ₂₆ ClF ₄ N ₃ O ₃	516	6	18
15	1370	C ₂₄ H ₂₆ ClF ₄ N ₃ O ₃	516	3	10
	1371	C ₂₄ H ₂₇ ClF ₃ N ₃ O ₃	498	2	95
	1372	C ₂₃ H ₂₈ CIN ₃ O ₃	430	4	95
20	1373	C ₂₄ H ₃₀ CIN ₃ O ₂	428	9	42
	1374	C ₂₅ H ₃₂ CIN ₃ O ₂	442	10	47
	1375	C ₂₅ H ₂₉ ClF ₃ N ₃ O ₂	496	10	42
25	1376	C ₂₅ H ₃₂ CIN ₃ O ₄ S	506	8	32
	1377	C ₂₄ H ₂₉ BrCIN ₃ O ₂	506	9	35
	1378	C ₂₅ H ₂₉ ClF ₃ N ₃ O ₃	512	6	22
30	1379	C ₂₅ H ₂₈ ClF ₄ N ₃ O ₂	514	3	10
	1380	C ₂₅ H ₂₈ ClF ₄ N ₃ O ₂	514	10	37
	1381	C ₂₅ H ₂₉ ClF ₃ N ₃ O ₂	496	8	33
35	1382	C ₂₆ H ₃₆ CIN ₃ O ₃	474	10	41
	1383	C ₂₃ H ₃₀ CIN ₃ O ₂ S ₂	480	12	50
	1384	C ₂₇ H ₃₈ CIN ₃ O ₃	488	14	57
40	1385	C ₂₉ H ₃₄ CIN ₃ O ₃	508	12	49
	1386	C ₂₄ H ₂₉ ClF ₃ N ₃ O ₃	500	22	87
	1387	C ₂₄ H ₂₈ Cl ₂ N ₄ O ₄	507	6	22
45	1388	C ₂₄ H ₂₉ Cl ₂ N ₃ O ₂	462	10	46
	1389	C ₂₄ H ₂₉ CIN ₄ O ₄	473	15	65
	1390	C ₂₆ H ₃₁ CIN ₄ O ₂	467	7*	20
50	1391	C ₂₅ H ₃₂ CIN ₃ O ₃	458	8*	23
	1392	C ₂₆ H ₃₄ CIN ₃ O ₃	472	7*	19
	1393	C ₂₆ H ₃₁ ClF ₃ N ₃ O ₂	510	7*	17
55	1394	C ₂₆ H ₃₄ CIN ₃ O ₄	488	6*	17
	1395	C ₂₄ H ₂₈ CIN ₃ O ₂	426	22	9
	1396	C ₂₅ H ₃₀ CIN ₃ O ₂	440	21	94
	1397	C ₂₅ H ₂₇ ClF ₃ N ₃ O ₂	494	4*	14
	1398	C ₂₅ H ₃₀ CIN ₃ O ₄ S	504	9	35
	1399	C ₂₄ H ₂₇ Cl ₂ N ₃ O ₂	460	5*	16

Notes: * indicates "yield (mg) of trifluoroacetate".
Q means "Quantitative".

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Table 27 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	1400	C ₂₄ H ₂₇ ClN ₄ O ₄	471	3*	10
	1401	C ₂₅ H ₂₇ ClF ₃ N ₃ O ₃	510	5*	16
	1402	C ₂₅ H ₂₆ ClF ₄ N ₃ O ₂	511	5*	16
10	1403	C ₂₅ H ₂₆ ClF ₄ N ₃ O ₂	512	5*	16
	1404	C ₂₅ H ₂₇ ClF ₃ N ₃ O ₂	494	6*	21
	1405	C ₂₃ H ₂₈ ClN ₃ O ₂ S ₂	478	4*	14
15	1406	C ₂₇ H ₃₆ ClN ₃ O ₃	486	7*	29
	1407	C ₂₉ H ₃₂ ClN ₃ O ₃	506	3	13
	1408	C ₂₄ H ₂₇ ClF ₃ N ₃ O ₃	498	3*	11
20	1409	C ₂₄ H ₂₆ Cl ₂ N ₄ O ₄	505	5*	15
	1410	C ₂₆ H ₂₉ ClN ₄ O ₂	465	12	41
	1411	C ₂₅ H ₃₀ ClN ₃ O ₃	456	5*	15
25	1412	C ₂₆ H ₃₂ ClN ₃ O ₃	470	6*	16
	1413	C ₂₆ H ₂₉ ClF ₃ N ₃ O ₂	508	8*	20
	1414	C ₂₆ H ₃₂ ClN ₃ O ₄	486	6*	15
30	1415	C ₂₄ H ₂₇ BrClN ₃ O ₂	506	5*	14
	1416	C ₂₇ H ₃₂ ClN ₅ O ₃	510	29.7	Q
	1417	C ₂₆ H ₃₃ ClN ₄ O ₃	485	29.9	Q
35	1418	C ₂₅ H ₃₀ Cl ₂ N ₄ O ₃	505	30.2	Q
	1419	C ₃₀ H ₃₅ ClN ₄ O ₄	551	31.0	Q
	1420	C ₂₅ H ₂₉ Cl ₂ N ₅ O ₅	550	30.4	Q
40	1421	C ₂₄ H ₃₁ ClN ₄ O ₃ S ₂	523	25.0	88
	1422	C ₂₆ H ₃₀ ClF ₃ N ₄ O ₃	539	20.5	70
	1423	C ₂₆ H ₃₀ ClF ₃ N ₄ O ₄	555	22.7	75
45	1424	C ₂₆ H ₂₉ ClF ₄ N ₄ O ₃	557	25.8	85
	1425	C ₂₆ H ₃₀ ClF ₃ N ₄ O ₃	539	25.3	86
	1426	C ₂₆ H ₂₉ ClF ₄ N ₄ O ₃	557	26.8	88
50	1427	C ₂₅ H ₃₀ BrClN ₄ O ₃	551	27.1	90
	1428	C ₂₇ H ₂₉ ClF ₆ N ₄ O ₃	607	13.9	42
	1429	C ₂₅ H ₃₀ ClN ₅ O ₅	516	14.1	51
55	1430	C ₂₄ H ₂₈ Cl ₂ N ₄ O ₅	523	40	86
	1431	C ₂₃ H ₃₀ ClN ₃ O ₃ S ₂	496	41	93
	1432	C ₂₆ H ₃₁ ClN ₄ O ₃	483	43	Q
	1433	C ₂₇ H ₃₈ ClN ₃ O ₄	503	37	83
	1434	C ₂₉ H ₃₄ ClN ₃ O ₄	524	28	61
	1435	C ₂₄ H ₂₉ ClF ₃ N ₃ O ₄	516	40	87

Notes: * indicates "yield (mg) of trifluoroacetate".

Q means "Quantitative".

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Table 27 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	1436	C ₂₆ H ₃₁ ClN ₄ O ₃	483	31	72
	1437	C ₂₅ H ₂₉ ClF ₃ N ₃ O ₄	528	40	86
	1438	C ₂₅ H ₂₈ ClF ₄ N ₃ O ₃	530	45	97
10	1439	C ₂₅ H ₂₈ ClF ₄ N ₃ O ₃	530	35	74
	1440	C ₂₄ H ₂₉ BrClN ₃ O ₃	523	45	98
	1441	C ₂₄ H ₂₉ Cl ₂ N ₃ O ₃	478	38	91
15	1442	C ₂₄ H ₂₉ ClN ₄ O ₅	488	38	87
	1443	C ₂₅ H ₂₉ ClF ₃ N ₃ O ₃	512	42	93
	1444	C ₂₄ H ₃₀ ClN ₃ O ₃	444	43	Q
20	1445	C ₂₅ H ₃₂ ClN ₃ O ₃	458	37	91
	1446	C ₂₅ H ₂₉ ClF ₃ N ₃ O ₃	512	41	91
	1447	C ₂₆ H ₃₄ ClN ₃ O ₄	488	34	78
25	1448	C ₂₇ H ₃₆ ClN ₃ O ₆	534	37	71
	1449	C ₂₇ H ₃₀ ClF ₆ N ₃ O ₂	578	17	48
	1450	C ₂₆ H ₃₄ ClN ₃ O ₂	456	7.6*	23
30	1451	C ₂₇ H ₃₃ ClF ₃ N ₃ O ₂	524	6	15
	1452	C ₂₇ H ₃₆ ClN ₃ O ₂	470	8	24
	1453	C ₂₇ H ₃₆ ClN ₃ O ₃	486	9	24
35	1454	C ₂₈ H ₃₈ ClN ₃ O ₃	500	4	10
	1455	C ₂₇ H ₃₃ ClF ₃ N ₃ O ₃	540	9	23
	1456	C ₂₈ H ₃₈ ClN ₃ O ₂	484	7	21
40	1457	C ₂₈ H ₃₈ ClN ₃ O ₄	516	11	30
	1458	C ₂₉ H ₄₀ ClN ₃ O ₅	547	9	23
	1459	C ₃₀ H ₄₂ ClN ₃ O ₄	544	8	21
45	1460	C ₃₂ H ₄₆ ClN ₃ O ₅	589	7	17
	1461	C ₂₅ H ₃₁ ClN ₄ O ₃	471	25	79
	1462	C ₂₆ H ₃₃ ClN ₄ O ₄	501	35	97
50	1463	C ₂₇ H ₃₅ ClN ₄ O ₄	515	35	9
	1464	C ₂₇ H ₃₅ ClN ₄ O ₃	499	32	54
	1465	C ₂₇ H ₃₅ ClN ₄ O ₅	531	27	77
55	1466	C ₂₈ H ₃₇ ClN ₄ O ₆	561	14	37
	1467	C ₂₉ H ₃₉ ClN ₄ O ₅	559	24	66
	1468	C ₃₁ H ₄₃ ClN ₄ O ₆	603	25	65
	1469	C ₂₆ H ₃₄ ClN ₃ O ₄	488	13.0*	39
	1470	C ₂₈ H ₃₈ ClN ₃ O ₅	532	13.4*	37
	1471	C ₂₅ H ₃₂ ClN ₃ O ₄	474	12.7*	40

Notes: * indicates "yield (mg) of trifluoroacetate".
Q means "Quantitative".

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Table 27 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	1472	C ₂₆ H ₂₈ ClF ₆ N ₃ O ₄	596	13.8*	34
	1473	C ₂₅ H ₃₂ ClN ₃ O ₄	474	14.2*	37
	1474	C ₂₅ H ₃₂ ClN ₃ O ₂	442	11.5*	32
10	1475	C ₂₆ H ₃₄ ClN ₃ O ₅	504	12.0*	30
	1476	C ₂₇ H ₃₆ ClN ₃ O ₄	502	14.7*	37
	1477	C ₂₉ H ₄₀ ClN ₃ O ₅	546	13.5*	32
15	1478	C ₂₆ H ₃₄ ClN ₃ O ₄	488	11.9*	31
	1479	C ₂₇ H ₃₀ ClF ₆ N ₃ O ₄	610	14.6*	31
	1480	C ₂₅ H ₃₂ ClN ₃ O ₃	458	14.0*	38
20	1481	C ₂₄ H ₂₇ ClF ₃ N ₃ O ₃	498	14.0*	35
	1482	C ₂₄ H ₃₀ ClN ₃ O ₃	444	10.4*	29
	1483	C ₂₅ H ₃₂ ClN ₃ O ₄	474	14.9*	39
25	1484	C ₂₅ H ₃₂ ClN ₃ O ₂	442	13.3*	37
	1485	C ₂₆ H ₃₄ ClN ₃ O ₅	504	13.7*	34
	1486	C ₂₇ H ₃₆ ClN ₃ O ₄	502	16.7*	42
30	1487	C ₂₉ H ₄₀ ClN ₃ O ₅	547	15.5*	36
	1488	C ₂₆ H ₃₄ ClN ₃ O ₄	488	14.1*	36
	1489	C ₂₇ H ₃₀ ClF ₆ N ₃ O ₄	610	17.5*	37
35	1490	C ₂₅ H ₃₂ ClN ₃ O ₃	458	15.1*	41
	1491	C ₂₄ H ₂₇ ClF ₃ N ₃ O ₃	498	15.4*	39
	1492	C ₂₄ H ₃₀ ClN ₃ O ₃	444	12.7*	35
40	1493	C ₂₂ H ₂₆ BrClN ₄ O ₂	495	10.4*	25
	1494	C ₂₂ H ₂₆ Cl ₂ N ₄ O ₂	449	11.1*	29
	1495	C ₂₃ H ₂₉ ClN ₄ O ₂	429	5.2*	14
45	1496	C ₂₃ H ₂₉ ClN ₄ O ₃	445	12.4*	33
	1497	C ₂₂ H ₂₅ Cl ₃ N ₄ O ₂	483	10.0*	25
	1498	C ₂₄ H ₃₁ ClN ₄ O ₂	443	12.1*	32
50	1499	C ₂₅ H ₃₃ ClN ₄ O ₅	505	16.1*	39
	1500	C ₂₃ H ₂₈ BrClN ₄ O ₂	507	12.0*	29
	1501	C ₂₈ H ₃₈ ClN ₃ O ₄	516	39.2*	Q
55	1502	C ₂₈ H ₃₈ ClN ₃ O ₂	484	34.0*	Q
	1503	C ₂₉ H ₄₀ ClN ₃ O ₅	546	14.5*	39
	1504	C ₃₀ H ₄₂ ClN ₃ O ₄	544	11.8*	32
	1505	C ₃₂ H ₄₆ ClN ₃ O ₅	588	12.2*	31
	1506	C ₂₉ H ₄₀ ClN ₃ O ₄	530	44.5*	Q
	1507	C ₃₀ H ₃₆ ClF ₆ N ₃ O ₄	652	46.0*	Q

Notes: * indicates "yield (mg) of trifluoroacetate".
Q means "Quantitative".

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Table 27 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	1508	C ₂₈ H ₃₈ ClN ₃ O ₃	500	11.2*	Q
	1509	C ₂₇ H ₃₆ ClN ₃ O ₃	486	35.5*	Q
	1510	C ₂₇ H ₃₃ ClF ₃ N ₃ O ₃	540	41.4*	Q
10	1511	C ₂₉ H ₄₀ ClN ₃ O ₄	530	13.6*	37
	1512	C ₃₀ H ₃₆ ClF ₆ N ₃ O ₄	652	44.2*	Q
	1513	C ₂₈ H ₃₈ ClN ₃ O ₃	500	39.9*	Q
15	1514	C ₂₇ H ₃₆ ClN ₃ O ₃	486	12.0*	35
	1515	C ₂₇ H ₃₃ ClF ₃ N ₃ O ₃	540	37.8*	Q
	1516	C ₂₈ H ₃₈ ClN ₃ O ₄	516	12.3*	34
20	1517	C ₂₈ H ₃₈ ClN ₃ O ₂	484	30.7*	90
	1518	C ₂₉ H ₄₀ ClN ₃ O ₅	546	13.8*	37
	1519	C ₃₀ H ₄₂ ClN ₃ O ₄	544	13.1*	35
25	1520	C ₃₂ H ₄₆ ClN ₃ O ₅	589	14.1*	35
	1521	C ₂₉ H ₃₄ ClN ₃ O ₃ S ₂	572	38.3	93
	1522	C ₃₂ H ₃₅ ClN ₄ O ₃	559	39.6	98
30	1523	C ₃₃ H ₄₂ ClN ₃ O ₄	580	40.9	98
	1524	C ₃₅ H ₃₈ ClN ₃ O ₄	600	40.5	94
	1525	C ₃₀ H ₃₃ ClF ₃ N ₃ O ₄	592	38.7	91
35	1526	C ₃₁ H ₃₃ ClF ₃ N ₃ O ₄	604	38	87
	1527	C ₃₀ H ₃₃ ClN ₄ O ₅	565	38.5	94
	1528	C ₃₁ H ₃₃ ClF ₃ N ₃ O ₃	588	35.8	84
40	1529	C ₃₀ H ₃₄ ClN ₃ O ₃	520	34.7	93
	1530	C ₃₁ H ₃₆ ClN ₃ O ₃	534	38.4	Q
	1531	C ₃₂ H ₃₈ ClN ₃ O ₄	564	39.3	97
45	1532	C ₃₃ H ₄₀ ClN ₃ O ₆	610	45.5	Q
	1533	C ₂₈ H ₃₆ ClN ₃ O ₃	498	4.1*	10
	1534	C ₂₈ H ₃₆ ClN ₃ O ₃	498	6.4*	16
50	1535	C ₃₀ H ₃₂ Cl ₂ N ₄ O ₅	599	3.4*	8
	1536	C ₃₀ H ₃₂ BrClN ₄ O ₅	644	3.4*	7
	1537	C ₃₂ H ₃₅ ClN ₄ O ₃	559	1.6*	4
55	1538	C ₃₁ H ₃₂ ClF ₄ N ₃ O ₃	606	4.3*	10
	1539	C ₃₁ H ₃₂ ClF ₄ N ₃ O ₃	606	5.9*	14
	1540	C ₃₀ H ₃₃ BrClN ₃ O ₃	599	5.7*	13
	1541	C ₃₀ H ₃₃ Cl ₂ N ₃ O ₃	554	6.4*	16
	1542	C ₃₁ H ₃₃ ClF ₃ N ₃ O ₃	588	6.3*	15
	1543	C ₂₇ H ₃₄ ClN ₃ O ₃	484	1.8*	4

Notes: * indicates "yield (mg) of trifluoroacetate".
Q means "Quantitative".

[Example 1544] Synthesis of 1-(4-chlorobenzyl)-4-[[N-(3,5-bis(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (Compd. No. 1213)

[0266] A dichloromethane (1 mL) solution of 3,5-bis(trifluoromethyl)benzoyl chloride (0.058 mmol) was added to a mixture of 1-(4-chlorobenzyl)-4-[(glycylamino)methyl]piperidine (0.050 mmol) with chloroform (0.2 mL), a piperidinomethylpolystyrene (58 mg) and dichloromethane (0.75 mL). The resulting reaction mixture was stirred at room temperature for 2 hours, and methanol (1.0 mL) was then added to the obtained mixture. The resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was loaded onto a Varian™ SCX column and washed with methanol (16 mL). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (6 mL) and concentrated to thereby provide 1-(4-chlorobenzyl)-4-[[N-(3,5-bis(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (Compd. No. 1213) (24.0 mg, 90%). The purity was determined by RPLC/MS (100%). ESI/MS m/e 536.2 (M⁺+H, C₂₄H₂₄ClF₆N₃O₂).

[Examples 1545 to 1547]

[0267] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1544. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 28.

Table 28

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1545	1214	C ₂₃ H ₂₄ ClF ₄ N ₃ O ₃	486.2	22.2	91
1546	1215	C ₂₂ H ₂₄ Cl ₃ N ₃ O ₂	467.9	20.9	89
1547	1216	C ₂₂ H ₂₄ ClF ₂ N ₃ O ₂	436.0	19.3	89

[Example 1548] Synthesis of 4-[[N-(3-bromo-4-methylbenzoyl)glycyl]aminomethyl]-1-(4-chlorobenzyl)piperidine (Compd. No. 1113)

[0268] 3-Bromo-4-methylbenzoic acid (0.060 mmol), diisopropylcarbodiimide (0.060 mmol) and HOBt (0.060 mmol) were added to a solution of 1-(4-chlorobenzyl)-4-[(glycylamino)methyl]piperidine (0.050 mmol) in chloroform (1.35 mL) and tert-butanol (0.15 mL). The resulting reaction mixture was stirred at room temperature for 15 hours. The mixture was then loaded onto a Varian™ SCX column and washed with methanol/chloroform = 1:1 (12 mL) and methanol (12 mL). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated to thereby afford 4-[[N-(3-bromo-4-methylbenzoyl)glycyl]aminomethyl]-1-(4-chlorobenzyl)piperidine (Compd. No. 1113) (16.1 mg, 65%). The purity was determined by RPLC/MS (95%). ESI/MS m/e 494.0 (C₂₃H₂₇BrClN₃O₂).

[Examples 1549 to 1619]

[0269] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of 1548. The obtained products, if necessary, were purified by preparative TLC to provide the objective compounds. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 29.

[0270] Compd. No. 1422 was obtained as a by-product of Compd. No. 1418: 5.6 mg, yield: 25%; ESI/MS m/e 447.2 (C₂₂H₂₇ClN₄O₂S).

Table 29

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1549	1114	C ₂₂ H ₂₄ BrClFN ₃ O ₂	498.0	20.2	81
1550	1115	C ₂₂ H ₂₄ Cl ₂ FN ₃ O ₂	452.2	18.6	82
1551	1116	C ₂₃ H ₂₇ ClIN ₃ O ₂	539.1	21.9	81
1552	1117	C ₂₃ H ₂₇ ClN ₄ O ₄	459.2	18.7	81
1553	1187	C ₂₃ H ₂₇ BrClN ₃ O ₂	494.0	22.1	90
1554	1188	C ₂₄ H ₂₇ ClN ₄ O ₃	455.2	17.2	76

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Table 29 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	1555	C ₂₅ H ₂₉ ClN ₄ O ₃	469.2	21.1	90
	1556	C ₂₂ H ₂₆ ClFN ₄ O ₂	433.2	20.4	94
	1557	C ₂₃ H ₂₄ Cl ₂ F ₃ N ₃ O ₂	502.0	22.5	90
10	1558	C ₂₃ H ₂₇ ClFN ₃ O ₂	432.2	21.2	98
	1559	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₂	448.0	21.6	96
	1560	C ₂₂ H ₂₆ ClIN ₄ O ₂	541.0	26.4	98
15	1561	C ₂₂ H ₂₅ ClF ₂ N ₄ O ₂	451.0	21.3	94
	1562	C ₂₁ H ₂₇ ClN ₄ O ₂	403.2	19.4	96
	1563	C ₂₈ H ₃₀ ClN ₃ O ₂ S	524.0	24.7	94
20	1564	C ₂₂ H ₂₅ ClN ₄ O ₅	461.0	20.7	90
	1565	C ₂₅ H ₂₆ ClF ₃ N ₄ O ₃	523.2	25.0	96
	1566	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₃	464.2	12.2	53
25	1567	C ₂₂ H ₂₅ BrClN ₃ O ₃	496.0	24.1	97
	1568	C ₂₂ H ₂₅ Cl ₂ N ₃ O ₃	450.2	21.8	97
	1569	C ₂₂ H ₂₄ BrCl ₂ N ₃ O ₂	514.0	27.2	Q
30	1570	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₂	448.0	21.4	95
	1571	C ₂₂ H ₂₄ Cl ₂ IN ₃ O ₂	560.0	27.0	96
	1572	C ₂₃ H ₂₈ ClN ₃ O ₂	430.2	23.8	Q
35	1573	C ₂₂ H ₂₅ ClIN ₃ O ₃	542.0	29.4	Q
	1574	C ₂₁ H ₂₆ ClN ₃ O ₂ S	420.0	13.0	62
	1575	C ₂₄ H ₂₈ BrClN ₄ O ₃	537.2	5.2	19
40	1576	C ₂₃ H ₂₆ ClN ₅ O ₂	440.2	21.8	99
	1577	C ₂₃ H ₂₄ Cl ₂ F ₃ N ₃ O ₂	502.0	20.0	80
	1578	C ₂₀ H ₂₃ BrClN ₃ O ₂ S	486.0	21.0	87
45	1579	C ₂₈ H ₃₀ ClN ₃ O ₄ S	540.2	23.8	88
	1580	C ₂₈ H ₃₀ ClN ₃ O ₂	476.0	20.0	84
	1581	C ₂₄ H ₂₈ Cl ₂ N ₄ O ₃	491.0	0.8	3
50	1582	C ₂₃ H ₂₆ ClN ₅ O ₂ S	472.0	10.4	44
	1583	C ₂₉ H ₃₀ ClN ₃ O ₃	504.2	26.8	Q
	1584	C ₂₃ H ₂₆ ClF ₃ N ₄ O ₂	483.2	16.5	68
55	1585	C ₂₃ H ₂₆ ClF ₃ N ₄ O ₃	499.0	20.0	80
	1586	C ₂₁ H ₂₄ BrClN ₄ O ₂	481.0	18.1	75
	1587	C ₂₁ H ₂₄ Cl ₂ N ₄ O ₂	435.0	5.5	25
	1588	C ₂₇ H ₃₀ ClN ₃ O ₃	492.0	18.6	76
	1589	C ₂₁ H ₂₇ ClN ₄ O ₂	415.2	18.1	87
	1590	C ₂₃ H ₂₅ N ₃ O ₂ S	500.0	18.3	73
	1591	C ₂₂ H ₂₆ Cl ₂ N ₄ O ₂	449.0	366.0	83
	1592	C ₂₄ H ₂₉ F ₃ N ₄ O ₂ S	495.2	13.7	55

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Table 29 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1593	1665	C ₂₄ H ₂₉ F ₃ N ₄ O ₃ S	511.2	14.9	58
1594	1666	C ₂₃ H ₂₈ F ₂ N ₄ O ₂ S	463.2	12.9	56
1595	1667	C ₂₂ H ₂₇ Br ₂ N ₃ O ₃	542	26.1	96
1596	1668	C ₂₄ H ₃₀ F ₂ N ₄ O ₂	445	22.9	Q
1597	1669	C ₂₄ H ₃₁ FN ₄ O ₂	427	24.0	Q
1598	1670	C ₂₄ H ₃₁ IN ₄ O ₂	535	28.1	Q
1599	1671	C ₂₅ H ₃₁ F ₃ N ₄ O ₃	493	26.8	Q
1600	1672	C ₂₅ H ₃₁ F ₃ N ₄ O ₂	478	24.7	Q
1601	1673	C ₂₄ H ₂₉ BrClN ₃ O ₂	508	24.9	98
1602	1674	C ₂₀ H ₂₂ Br ₂ FN ₃ O ₃	532	25.6	96
1603	1675	C ₂₂ H ₂₅ F ₃ N ₄ O ₂	435	21.5	99
1604	1676	C ₂₂ H ₂₆ F ₂ N ₄ O ₂	417	21.4	Q
1605	1677	C ₂₂ H ₂₆ BrFN ₄ O ₂	479	23.4	98
1606	1678	C ₂₂ H ₂₆ FIN ₄ O ₂	525	27.4	Q
1607	1679	C ₂₂ H ₂₆ ClFN ₄ O ₂	433	22.4	Q
1608	1680	C ₂₃ H ₂₆ F ₄ N ₄ O ₃	483	25.5	Q
1609	1681	C ₂₃ H ₂₆ F ₄ N ₄ O ₂	467	23.2	99
1610	1682	C ₂₃ H ₂₆ BrClFN ₃ O	498	24.2	98
1611	1683	C ₂₇ H ₂₈ Br ₂ N ₄ O ₄	633	31.8	Q
1612	1684	C ₂₉ H ₃₁ F ₂ N ₅ O ₃	536	28.3	Q
1613	1685	C ₂₉ H ₃₂ FN ₅ O ₃	518	31.1	Q
1614	1686	C ₂₉ H ₃₂ BrN ₅ O ₃	578	29.6	Q
1615	1687	C ₂₉ H ₃₂ IN ₅ O ₃	626	32.4	Q
1616	1688	C ₂₉ H ₃₂ ClN ₅ O ₃	534	28.2	Q
1617	1689	C ₃₀ H ₃₂ F ₃ N ₅ O ₄	584	31.7	Q
1618	1690	C ₃₀ H ₃₂ F ₃ N ₅ O ₃	568	30.6	Q
1619	1691	C ₂₉ H ₃₀ BrClN ₄ O ₃	599	31.4	Q
Note: Q means "Quantitative".					

[0271] For example Compd. Nos. 1245 and 1600 exhibited the following NMR spectra.

[0272] Comps. No. 1245: ¹H NMR (270 MHz, CDCl₃) δ 1.20-1.97 (m, 7H), 2.80-2.86 (m, 2H), 3.19 (t, J = 6.5 Hz, 2H), 3.43 (s, 2H), 4.02 (d, J = 5.3 Hz, 2H), 5.52 (br s, 2H), 6.44 (d, J = 11.9, 6.6 Hz, 1H), 7.02 (br s, 1H), 7.21-7.32 (m, 5H).

[0273] Compd. No. 1600: ¹H NMR (270MHz, CDCl₃) δ 1.25-1.97 (m, 9H), 2.82-2.87 (m, 2H), 3.21 (t, J = 6.5 Hz, 2H), 3.44 (s, 2H), 4.06(d, J = 5.1 Hz, 2H), 5.98 (br s, 1H), 6.71 (d, J = 8.3 Hz, 1H), 6.87 (br s, 1H), 7.26 (s, 4H), 7.43 (dd, J = 5.9 Hz, 1H), 7.64 (s, 1H).

[Example 1620] Synthesis of 1-(4-chlorobenzyl)-4-[[N-(4-isopropylphenylsulfonyl)glycyl]aminomethyl]piperidine (Compd. No. 869)

[0274] A (piperidinomethyl)polystyrene resin (28 mg, 2.8 mmol/g) and 4-isopropylbenzenesulfonyl chloride (1.5 equivalents) were added to a chloroform (2 mL) solution of 1-(4-chlorobenzyl)-4-[(glycylamino)methyl]piperidine (14: 8 mg, 0.05 mmol). The resulting mixture was stirred at 25 °C for 16 hours, then filtered and concentrated to thereby afford 1-(4-chlorobenzyl)-4-[[N-(4-isopropylphenylsulfonyl)glycyl]aminomethyl]piperidine (Compd. No. 869) (22.1 mg,

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92%). The purity was determined by RPLC/MS (86%). ESI/MS m/e 478 ($M^+ + H$, $C_{24}H_{32}N_3O_3S$).

[Examples 1621 to 1627]

[0275] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1620. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 30.

Table 3.0

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1621	865	$C_{22}H_{28}ClN_3O_3S$	450	16.2	72
1622	866	$C_{22}H_{25}ClF_3N_3O_3S$	504	8.8	35
1623	867	$C_{23}H_{24}ClF_6N_3O_3S$	572	8.0	28
1624	868	$C_{23}H_{30}ClN_3O_3S$	464	9.6	41
1625	870	$C_{22}H_{28}ClN_3O_3S$	450	8.8	39
1626	871	$C_{25}H_{34}ClN_3O_3S$	492	11.1	45
1627	872	$C_{21}H_{26}ClN_3O_3S$	436	9.6	44

[Example 1628] Synthesis of 1-(4-chlorobenzyl-4-[[2-(3-(4-trifluoromethylphenyl)ureido)acetyl]amino]methyl]piperidine (Compd. No. 852)

[0276] A (piperidinomethyl)polystyrene resin (28 mg, 2.8 mmol/g) and 3-(trifluoromethyl)phenyl isocyanate (1.3 equivalents) were added to a chloroform (2 mL) solution of 1-(4-chlorobenzyl)-4-[(glycylamino)methyl]piperidine (14.8 mg, 0.05 mmol). The resulting mixture was stirred at 25 °C for 16 hours, and an (aminomethyl)polystyrene resin was added to the obtained mixture. The resulting mixture was stirred at 25 °C for 16 hours to trap the remaining isocyanate. The obtained mixture was filtered and concentrated to thereby provide 1-(4-chlorobenzyl)-4-[[2-(3-(4-trifluoromethylphenyl)ureido)acetyl]amino]methyl]piperidine (Compd. No. 852) (19 mg, 78%). The purity was determined by RPLC/MS (92%). ESI/MS m/e 483 ($M^+ + H$, $C_{23}H_{26}ClF_3N_4O_2$).

[Examples 1629 to 1641]

[0277] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1628. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 31.

Table 31

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1629	851	$C_{23}H_{26}ClF_3N_4O_2$	483	13.2	55
1630	853	$C_{22}H_{27}ClN_4O_2$	416	8.5*	32
1631	854	$C_{23}H_{29}ClN_4O_2$	429	11.4*	42
1632	855	$C_{23}H_{29}ClN_4O_2$	429	10.1*	37
1633	856	$C_{24}H_{29}ClN_4O_3$	457	10.3*	36
1634	857	$C_{23}H_{29}ClN_4O_3$	445	10.9*	39
1635	858	$C_{23}H_{29}ClN_4O_3$	445	8.6*	31
1636	859	$C_{22}H_{26}Cl_2N_4O_2$	449	11.0*	39
1637	860	$C_{23}H_{26}ClN_5O_2$	440	9.2*	33
1638	861	$C_{22}H_{27}ClN_4OS$	431	13.3	62

Note: * indicates "yield (mg) of trifluoroacetate".

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Table 31 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1639	862	C ₂₃ H ₂₉ ClN ₄ OS	445	15.3	69
1640	863	C ₂₃ H ₂₉ ClN ₄ O ₂ S	461	14.7	64
1641	864	C ₂₃ H ₂₉ ClN ₄ O ₂ S	461	13.1	57

[Example 16.42] Synthesis of 1-(4-chlorobenzyl)-4-[[N-(3-ethoxybenzoyl)-D-phenylalanyl]aminomethyl]piperidine (Compd. No. 2091)

[0278] Triethylamine (0.090 mL), N-(tert-butoxycarbonyl)-D-(phenylalanine) (122 mg), EDCI (89 mg) and HOBt (62 mg) were added to a chloroform (3 mL) solution of 1-(4-chlorobenzyl)-4-(aminomethyl)piperidine (100 mg). The resulting mixture was stirred at room temperature for 17 hours, and the reaction mixture was washed with a 1 M aqueous solution of NaOH (2 mL×2) and brine (2 mL). The organic layer was dried and concentrated to thereby afford 1-(4-chlorobenzyl)-4-[[N-(tert-butoxycarbonyl)-D-phenylalanyl]aminomethyl]piperidine.

[0279] The resulting 1-(4-chlorobenzyl)-4-[[N-(tert-butoxycarbonyl)-D-phenylalanyl]aminomethyl]piperidine was dissolved in methanol (5 mL), and a 4 M dioxane solution of HCl was then added to the solution. The obtained solution was stirred at room temperature for 19 hours and concentrated.

[0280] Triethylamine (0.090 mL), EDCI (90 mg) and HOBt (68 mg) were added to a chloroform solution (1 mL) of the obtained residue and 3-ethoxybenzoic acid (80 mg, 0.48 mmol). The resulting mixture was stirred at room temperature for 17 hours. The resulting reaction mixture was washed with a 1 M aqueous solution of NaOH (1.5 mL×2) and brine (1.5 mL). The organic layer was dried, concentrated and purified by column chromatography (SiO₂, dichloromethane/methanol = 95:5) to provide 1-(4-chlorobenzyl)-4-[[N-(3-ethoxybenzoyl)-D-phenylalanyl]aminomethyl]piperidine (Compd. No. 2091) (183.5 mg, 82%). The purity was determined by RPLC/MS (99%). ESI/MS m/e 534.0 (M⁺+H, C₃₁H₃₆ClN₃O₃).

[Examples 1643 to 1657]

[0281] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of 1642. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 32.

Table 32

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1643	2092	C ₃₃ H ₃₇ ClN ₄ O ₃	572.8	152.9	64
1644	2093	C ₂₇ H ₃₆ ClN ₃ O ₃ S	518.0	177.4	82
1645	2094	C ₂₉ H ₃₄ ClN ₃ O ₃ S	539.9	164.4	73
1646	2095	C ₂₈ H ₃₈ ClN ₃ O ₃	500.0	139.1	66
1647	2096	C ₃₁ H ₄₂ ClN ₃ O ₃	540.0	161.7	71
1648	2097	C ₂₇ H ₃₆ ClN ₃ O ₃	485.8	157.8	78
1649	2098	C ₃₁ H ₃₅ Cl ₂ N ₃ O ₃	567.9	172.2	72
1650	2099	C ₃₀ H ₃₄ ClN ₃ O ₃	519.8	144.7	66
1651	2100	C ₃₂ H ₃₈ ClN ₃ O ₄	564.0	181.5	77
1652	2101	C ₃₈ H ₄₂ ClN ₃ O ₄	639.9	192.3	72
1653	2103	C ₃₃ H ₄₀ ClN ₃ O ₄	577.8	159.9	66
1654	2104	C ₂₈ H ₃₆ ClN ₃ O ₅	530.1	99.7	45
1655	2115	C ₂₇ H ₃₆ ClN ₃ O ₃	486.2	122.9	60
1656	2116	C ₂₈ H ₃₈ ClN ₃ O ₃	500.1	118.3	57
1657	2117	C ₂₈ H ₃₄ ClN ₅ O ₃	524.1	98.3	45

[Reference Example 29] Synthesis of 1-(tert-butoxycarbonyl)-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine

[0282] N-[3-(Trifluoromethyl)benzoyl]glycine (4.22 g, 17.0 mmol), EDCI (4.25 g, 22.1 mmol), 1-hydroxybenzotriazole hydrate (2.99 g, 22.1 mmol) and triethylamine (1.72 g) were added to an anhydrous dichloromethane (200 mL) solution of 1-(tert-butoxycarbonyl)-4-(aminomethyl)piperidine (4.03 g). The resulting reaction mixture was stirred at 25 °C for 20 hours, and H₂O (100 mL) was then added to the mixture. The obtained mixture was extracted with dichloromethane (50 mL×2). The extracts were combined, washed with H₂O (50 mL×2) and brine (50 mL), dried (over MgSO₄) and concentrated to thereby afford a yellow oil. The obtained crude product was purified by column chromatography (SiO₂, 70% ethyl acetate-hexane) to provide 1-(tert-butoxycarbonyl)-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine as a white solid (6.39 g, 85%). ¹H NMR(CDCl₃, 300MHz) δ 1.4 (s, 9H), 1.0-1.8(m, 5H), 2.6-2.8 (m, 2H), 3.15-3.3 (m, 2H), 4.0-4.3 (m, 4H), 6.6-6.7 (m, 1H), 7.64(s, 1H), 7.60 (dd, 1H, J = 7.2, 7.2 Hz), 7.79 (d, 1H, J = 7.2 Hz), 8.0 (d, 1H, J = 7.2 Hz), 8.11 (s, 1H). The purity was determined by RPLC/MS (97%). ESI/MS m/e 444.3 (M⁺+H, C₂₁H₂₈N₃O₄).

[Reference Example 30] Synthesis of 4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine

[0283] A 1 M HCl-Et₂O (55 mL) was added to a methanol (40 mL) solution of 1-(tert-butoxycarbonyl)-4-[[N-(3-trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine (2.29 g, 5.16 mmol). The obtained mixture was stirred at 25 °C for 15 hours, and the solvent was removed under reduced pressure. A 2 M aqueous solution of NaOH (100 mL) was added to the mixture, and the resulting mixture was extracted with ethyl acetate (100 mL×3). The extracts were combined, washed with brine (50 mL), dried (over K₂CO₃) and concentrated to thereby afford a white solid. The obtained crude solid was purified by column chromatography (SiO₂, methanol/dichloromethane/triethylamine = 7:6:1) to provide 4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine as a white solid (1.27 g, 72%). The purity was determined by RPLC/MS (98%). ESI/MS m/e 344.1 (M⁺+H, C₁₆H₂₀N₃O₂).

[Example 1658] Synthesis of 1-[3-(trifluoromethoxy)benzyl]-4-[(N-(3-(trifluoromethyl)benzoyl)glycyl)aminomethyl]piperidine (Compd. No. 927)

[0284] An acetonitrile (1.0 mL) solution of 4-[[N-(3-trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine (19.9 mg, 0.058 mmol) and a (piperidinomethyl)polystyrene (55 mg, 2.7 mmol base/g resin) were added to an acetonitrile (1.0 mL) solution of 3-(trifluoromethoxy)benzyl bromide (12.3 mg, 0.048 mmol). The obtained mixture was stirred at 60 °C for 2.5 hours. Phenyl isocyanate (6.9 mg, 0.048 mmol) was added to the cooled reaction mixture, and the resulting mixture was stirred at 25°C for 1 hour. The reaction mixture was loaded onto a Varian™ SCX column and washed with methanol (20 mL). The product was eluted with a 2 M methanol solution of NH₃ and concentrated to provide 1-[3-(trifluoromethoxy)benzyl]-4-[(N-(3-(trifluoromethyl)benzoyl)glycyl)aminomethyl]piperidine (Compd. No. 927) as an off-white oil (22.8 mg, 91%). The purity was determined by RPLC/MS (99%). ESI/MS m/e 518.1 (M⁺+H, C₂₄H₂₅F₆N₃O₃).

[Examples 1659 to 1710]

[0285] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1658. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 33.

Table 33

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1659	875	C ₂₃ H ₂₆ F ₃ N ₃ O ₂	434	6.3	40
1660	876	C ₂₃ H ₂₅ BrF ₃ N ₃ O ₂	512	4.3	23
1661	877	C ₂₄ H ₂₅ F ₃ N ₄ O ₂	459	11.3	68
1662	878	C ₂₃ H ₂₅ F ₃ N ₄ O ₄	479	8.3	48
1663	884	C ₂₅ H ₂₉ F ₃ N ₄ O ₃	491	10.8	61
1664	885	C ₂₄ H ₂₈ F ₃ N ₃ O ₄ S	512	9.0	49
1665	886	C ₂₃ H ₂₅ F ₄ N ₃ O ₂	452	12.7	78

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Table 33 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	1666	C ₂₄ H ₂₅ F ₆ N ₃ O ₂	502	13.9	77
	1667	C ₂₃ H ₂₆ F ₃ N ₃ O ₃	450	11.5	71
	1668	C ₂₉ H ₃₀ F ₃ N ₃ O ₂	510	12.4	68
10	1669	C ₂₇ H ₂₈ F ₃ N ₃ O ₂	484	12.0	69
	1670	C ₂₃ H ₂₄ Cl ₂ F ₃ N ₃ O ₂	502	11.4	63
	1671	C ₂₄ H ₂₈ F ₃ N ₃ O ₃	464	11.7	70
15	1672	C ₂₄ H ₂₆ F ₃ N ₅ O ₅	522	13.9	74
	1673	C ₂₆ H ₃₂ F ₃ N ₃ O ₃	492	11.3	64
	1674	C ₂₄ H ₂₈ F ₃ N ₃ O ₂	448	4.8	30
20	1675	C ₂₄ H ₂₅ F ₃ N ₄ O ₂	459	17.5	Q
	1676	C ₂₄ H ₂₆ F ₃ N ₃ O ₄	478	9.2	57
	1677	C ₂₄ H ₂₆ F ₃ N ₃ O ₄	478	8.9	55
25	1678	C ₂₄ H ₂₈ F ₃ N ₃ O ₃	464	13.7	82
	1679	C ₂₅ H ₂₈ F ₃ N ₃ O ₄	492	18.6	Q
	1680	C ₂₉ H ₃₀ F ₃ N ₃ O ₂	510	13.7	75
30	1681	C ₂₃ H ₂₄ F ₃ N ₅ O ₆	524	12.6	67
	1682	C ₂₅ H ₃₀ F ₃ N ₃ O ₄	494	14.0	79
	1683	C ₂₅ H ₃₀ F ₃ N ₃ O ₂	462	11.2	67
35	1684	C ₃₁ H ₃₄ F ₃ N ₃ O ₂	538	19.6	75
	1685	C ₃₀ H ₃₁ F ₃ N ₄ O ₃	553	30.4	76
	1686	C ₃₀ H ₃₁ F ₃ N ₄ O ₃	553	12.6	63
40	1687	C ₂₃ H ₂₄ Cl ₂ F ₃ N ₃ O ₂	502	11.0	61
	1688	C ₂₃ H ₂₅ ClF ₃ N ₃ O ₂	468	20.2	89
	1689	C ₂₃ H ₂₄ Br ₂ F ₃ N ₃ O ₂	590	20.2	95
45	1690	C ₂₄ H ₂₈ F ₃ N ₃ O ₃	464	12.6	76
	1691	C ₃₀ H ₃₂ F ₃ N ₃ O ₃	540	13.9	72
	1692	C ₂₄ H ₂₈ F ₃ N ₃ O ₃	464	8.3	25
50	1693	C ₂₂ H ₂₅ F ₃ N ₄ O ₂	435	2.5	8
	1694	C ₂₂ H ₂₅ F ₃ N ₄ O ₂	435	2.7	9
	1695	C ₂₆ H ₃₀ F ₃ N ₃ O ₄	506	3.9	22
55	1696	C ₂₄ H ₂₈ F ₃ N ₃ O ₂	448	15.9	99
	1697	C ₂₄ H ₂₅ F ₆ N ₃ O ₃	518	20.3	81
	1698	C ₂₇ H ₂₈ F ₃ N ₃ O ₂	484	15.5	89
55	1699	C ₂₀ H ₂₆ F ₃ N ₃ O ₂	398	7.3	51
	1700	C ₂₉ H ₂₉ ClF ₃ N ₃ O ₂	544	12.5	48
	1701	C ₂₄ H ₂₅ F ₆ N ₃ O ₃	518	21.4	86
55	1702	C ₂₄ H ₂₈ F ₃ N ₃ O ₂ S	480	23.7	Q
	1703	C ₂₄ H ₂₈ F ₃ N ₃ O ₂	448	21.3	99

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Table 33 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1704	931	C ₂₄ H ₂₅ F ₃ N ₄ O ₂	459	21.4	97
1705	932	C ₂₃ H ₂₄ ClF ₃ N ₄ O ₄	513	15.6	63
1706	933	C ₂₄ H ₂₈ F ₃ N ₃ O ₂	448	16.6	77
1707	934	C ₂₂ H ₂₅ F ₃ N ₄ O ₂	435	18.0	43
1708	935	C ₂₃ H ₂₅ F ₃ N ₄ O ₄	479	15.1	65
1709	936	C ₂₃ H ₂₅ F ₃ N ₄ O ₄	479	15.4	67
1710	1615	C ₂₄ H ₂₅ F ₆ N ₃ O ₂ S	534.2	26.3	99
Note: Q means "Quantitative".					

[Example 1711] Synthesis of 1-[4-(dimethylamino)benzyl]-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (Compd. No. 937)

[0286] A methanol (1.0 mL) solution of 4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (20.0 mg, 0.058 mmol) and NaBH₃CN (16.5 mg) were added to a 5% acetic acid solution (1.0 mL) of 4-(dimethylamino)benzaldehyde (30.4 mg, 0.204 mmol), and the resulting mixture was stirred at 60 °C for 19 hours. The solvent was evaporated to provide a solid. Acetonitrile (2.0 mL) and phenyl isocyanate (6.9 mg, 0.048 mmol) were added to the solid, and resulting mixture was stirred at 25 °C for 1 hour. The reaction mixture was loaded onto a Varian™ SCX column and washed with methanol (20 mL). The obtained crude product was eluted with a 2 M NH₃-methanol (6 mL), and the eluate was concentrated to thereby afford 1-[4-(dimethylamino)benzyl]-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (Compd. No. 937) as an off-white oil (13.5 mg, 49%). The purity was determined by RPLC/MS (87%). ESI/MS m/e 477.3 (M⁺+H, C₂₅H₃₁F₃N₄O₂).

[Examples 1712 to 1729]

[0287] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to Example 1711. The obtained products, if necessary, were purified by preparative TLC (SiO₂) to provide the objective compounds. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 34.

Table 34

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1712	879	C ₂₄ H ₂₆ F ₃ N ₃ O ₄	478	13.0	62
1713	880	C ₂₄ H ₂₆ F ₃ N ₃ O ₄	478	16.3	78
1714	881	C ₂₃ H ₂₅ BrF ₃ N ₃ O ₂	512	11.4	51
1715	882	C ₂₉ H ₃₀ F ₃ N ₃ O ₃	526	13.4	58
1716	883	C ₂₃ H ₂₅ ClF ₃ N ₃ O ₂	468	7.9	39
1717	904	C ₂₃ H ₂₆ F ₃ N ₃ O ₃	450	3.3	17
1718	905	C ₂₁ H ₂₃ F ₃ N ₄ O ₄ S	485	27.7	98
1719	938	C ₂₃ H ₂₄ ClF ₄ N ₃ O ₂	486	8.6	30
1720	939	C ₂₃ H ₂₄ ClF ₃ N ₄ O ₄	513	11.0	37
1721	940	C ₂₃ H ₂₆ F ₃ N ₃ O ₃	450	5.5	21
1722	941	C ₂₄ H ₂₄ ClF ₆ N ₃ O ₂	536	11.2	36
1723	987	C ₃₀ H ₃₂ F ₃ N ₃ O ₂	524	17.5	76
1724	1449	C ₂₅ H ₃₀ F ₃ N ₃ O ₂	462	21.6	80
1725	1450	C ₂₆ H ₃₂ F ₃ N ₃ O ₂	476	23.5	85

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Table 34 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1726	1452	C ₂₇ H ₃₅ F ₃ N ₄ O ₂	505	5.1	17
1727	1453	C ₂₆ H ₃₂ F ₃ N ₃ O ₃	492	22.0	77
1728	1454	C ₂₅ H ₃₀ F ₃ N ₃ O ₃	478	21.4	77
1729	1456	C ₂₅ H ₂₈ F ₃ N ₃ O ₄	492	23.8	83

[Example 1730] Synthesis of 1-[3-hydroxy-4-methoxybenzyl]-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (Compd. No. 1452)

[0288] A 5% acetic acid/methanol (1.0 mL) solution of 4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (20.0 mg, 0.058 mmol) and 3-hydroxy-4-methoxybenzaldehyde (33 mg) was added to a 5% acetic acid/methanol (1.0 mL) solution of NaBH₃CN (16.5 mg), and the mixture was stirred at 60 °C for 15 hours. The resulting reaction mixture was then loaded onto a Varian™ SCX column and washed with methanol (15 mL). The obtained crude product was eluted with a 2 M NH₃-methanol (5 mL) and concentrated to thereby afford 1-[3-hydroxy-4-methoxybenzyl]-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (Compd. No. 1452) (25.8 mg, 92%). The purity was determined by RPLC/MS (91%). ESI/MS m/e 480 (M⁺+H, C₂₄H₂₈F₃N₃O₄).

[Examples 1731 to 1733]

[0289] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1730. The obtained products, if necessary, were purified by preparative TLC to provide the objective compounds. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 35.

Table 35

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1731	1455	C ₂₄ H ₂₈ F ₃ N ₃ O ₄	480	24.0	86
1732	1647	C ₂₇ H ₃₄ F ₃ N ₃ O ₂	490.2	23.6	96
1733	1649	C ₂₆ H ₃₂ F ₃ N ₃ O ₂	476.2	23.1	97

[Example 1734] Synthesis of 1-(4-benzylbenzyl)-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (Compd. No. 926)

[0290] A chloroform (1.0 mL) solution of methanesulfonyl chloride (4.2 mg, 0.037 mmol) and a (piperidinomethyl) polystyrene (54 mg, 2.7 mmol base/g resin) were added to a chloroform (1.0 mL) solution of 4-(benzyl)benzyl alcohol (8.7 mg, 0.044 mmol), and the resulting mixture was stirred at 25°C for 15 hours. 4-[[N-(3-(Trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (15.1mg, 0.044 mmol) and KI (2 mg) were then added to the reaction mixture, and the resulting mixture solution was further stirred at 65 °C for 5 hours. Phenyl isocyanate (5.2 mg) was added to the cooled reaction mixture, and the obtained mixture was stirred at 25 °C for 1 hour. The resulting reaction mixture was loaded onto a Varian™ SCX column and washed with methanol (20 mL). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated to thereby afford 1-(4-benzylbenzyl)-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (Compd. No. 926) as an off-white oil (5.6 mg, 29%). The purity was determined by RPLC/MS (94%). ESI/MS m/e 524.1 (M⁺+H, C₃₀H₃₂F₃N₃O₂).

[Reference Example 31] Synthesis of 4-[[N-(benzyloxycarbonyl)glycyl]amino]methyl]-1-(tert-butoxycarbonyl)piperidine

[0291] Triethylamine (2.8 mL, 20 mmol), N-(benzyloxycarbonyl)glycine (3.77 g, 18 mmol), EDCI (3.45 g, 18 mmol) and HOBt (2.43 g, 18 mmol) were added to a chloroform (80 mL) solution of 4-(aminomethyl)-1-(tert-butoxycarbonyl)piperidine (3.54 g, 16.5 mmol). The resulting mixture was stirred at room temperature for 15 hours, and a 2 M aqueous solution of NaOH (100 mL) was then added to the mixture. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (100 mL×3). The organic layers were combined, dried over anhydrous sodium

sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography (SiO₂, ethyl acetate) to provide 4-[[N-(benzyloxycarbonyl)glycyl]amino]methyl]-1-(tert-butoxycarbonyl)piperidine as an amorphous solid (6.27 g, 94%).

5 [Reference Example 32] Synthesis of 4-[(glycylamino)methyl]-1-(tert-butoxycarbonyl)piperidine

10 **[0292]** A methanol (100 mL) solution of 4-[[N-(benzyloxycarbonyl)glycyl]amino]methyl]-1-(tert-butoxycarbonyl)piperidine (6.26 g, 15.4 mmol) was hydrogenated in the presence of a 5% palladium carbon (620 mg) at room temperature for 7 hours. The catalyst was removed by filtration through Celite, and the filtrate was then concentrated to thereby afford 4-[(glycylamino)methyl]-1-(tert-butoxycarbonyl)piperidine as a solid (3.84 g, 92%).

[Reference Example 33] Synthesis of 4-[[N-(2-amino-5-chlorobenzoyl)glycyl]amino]methyl]-1-(tert-butoxycarbonyl)piperidine

15 **[0293]** Triethylamine (0.75 mL, 5.4 mmol), 2-amino-5-chlorobenzoic acid (840 mg, 4.9 mmol), EDCI (940 mg, 4.9 mmol) and HOBt (660 mg, 4.9 mmol) were added to a chloroform (25 mL) solution of 4-[(glycylamino)methyl]-1-(tert-butoxycarbonyl)piperidine (1.33 g, 4.90 mmol). The resulting mixture was stirred at room temperature for 3 hours, and a 2 M aqueous solution of NaOH (20 mL) was then added to the mixture. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (20 mL×3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography (SiO₂, ethyl acetate) to thereby provide 4-[[N-(2-amino-5-chlorobenzoyl)glycyl]amino]methyl]-1-(tert-butoxycarbonyl)piperidine as a solid (1.63 g, 78%).

25 [Reference Example 34] Synthesis of 4-[[N-(2-amino-5-chlorobenzoyl)glycyl]amino]methyl]piperidine

30 **[0294]** A 4 M dioxane solution of HCl (9.5 mL) was added to a methanol (20 mL) solution of 4-[[N-(2-amino-5-chlorobenzoyl)glycyl]amino]methyl]-1-(tert-butoxycarbonyl)piperidine (1.63 g, 3.84 mmol), and the resulting mixture was stirred at room temperature for 6 hours. The reaction mixture was concentrated, and a 2 M aqueous solution of NaOH (20 mL) was added to the resulting residue. The obtained mixture was extracted with dichloromethane (20 mL×3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated to thereby afford 4-[[N-(2-amino-5-chlorobenzoyl)glycyl]amino]methyl]piperidine (1.19 g, 95%). ¹H NMR (CDCl₃, 270MHz) δ 1.10-1.76 (m, 4H), 2.55 (td, J = 2.4 and 12.2 Hz, 2H), 3.00-3.10 (m, 2H), 3.17 (t, J = 6.2 Hz, 2H), 3.48 (s, 2H), 4.03 (d, J = 4.9 Hz, 2H), 5.50 (br. s, 2H), 6.11-6.23 (m, 1H), 6.60 (d, J = 8.8 Hz, 1H), 6.85-7.02 (m, 1H), 7.15 (dd, J = 2.7 and 8.8 Hz, 1H), 7.38 (d, J = 2.4 Hz, 1H). ESI/MS m/e 325.2 (M⁺+H, C₁₅H₂₃ClN₄O₂).

35 **[0295]** Further, 4-[[N-(2-amino-5-bromobenzoyl)glycyl]amino]methyl]piperidine was synthesized by using the corresponding starting material and reactants according to Reference Examples 33 and 34. 951 mg, 64% (two steps); ESI/MS m/e 369.2 (M⁺+H, C₁₅H₂₁BrN₄O₂).

40 [Example 1735] Synthesis of 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]amino]methyl]-1-(4-chlorobenzyl)piperidine

45 **[0296]** Triethylamine (1.1 mL, 8 mmol), 2-(tert-butoxycarbonylamino)-4,5-difluorobenzoic acid (607 mg, 2.2 mmol), EDCI (422 mg, 2.2 mmol) and HOBt (337 mg, 2.2 mmol) were added to a dichloromethane (20 mL) solution of 1-(4-chlorobenzyl)-4-[(glycylamino)methyl]piperidine dihydrochloride (738 mg, 2 mmol), and the resulting mixture was stirred at room temperature for 14 hours. A 0.6 M aqueous solution of NaOH (50 mL) was then added to the mixture, and the obtained mixture was extracted with dichloromethane (3 times). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated to thereby provide 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]amino]methyl]-1-(4-chlorobenzyl)piperidine (1.01 g, 92%). ESI/MS m/e 551.3 (M⁺+H, C₂₇H₃₃ClF₂N₄O₄).

50 **[0297]** Moreover, 4-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]methyl]-1-(4-chlorobenzyl)piperidine was synthesized by using the corresponding starting material and reactants according to the above method. 3.03 g, 82%; ESI/MS m/e 583.2 (M⁺+H, C₂₈H₃₄ClF₃N₄O₄).

55 [Reference Example 35] Synthesis of 4-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]methyl]piperidine

[0298] A 5% formic acid/methanol solution (10 mL) of 1-(4-chlorobenzyl)-4-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]methyl]piperidine (447 mg, 0.93 mmol) and Pd(OH)₂ (60 mg, 0.23 mmol) was stirred at 50 °C for 14 hours. The palladium catalyst was removed by filtration through Celite, and the filtrate was concentrated. A 1 M aqueous

solution of NaOH (15 mL) was added to the resulting residue, and the obtained mixture was extracted with ethyl acetate (30 mL×3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography (SiO₂ ethyl acetate/methanol/triethylamine = 70:25:5) to thereby afford 4-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]methyl]piperidine (284 mg, 86%). ESI/MS m/e 359.0 (M⁺+H, C₁₆H₂₁F₃N₄O₂).

[0299] Furthermore, 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]amino]methyl]piperidine, 4-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethoxybenzoyl)glycyl]aminomethyl]piperidine and 4-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethoxybenzoyl)glycyl]amino]methyl]piperidine were synthesized by using the respective corresponding starting materials and reactants according to the above method.

[0300] 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]amino]methyl]piperidine: 564 mg, 89%; ESI/MS m/e 327.2 (M⁺+H, C₁₅H₂₀F₂N₄O₂).

[0301] 4-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethoxybenzoyl)glycyl]amino]methyl]piperidine: quantitative; ¹H NMR (CDCl₃, 400MHz) δ 1.10-1.25 (m, 2H), 1.45-1.73 (m, 3H), 1.51 (s, 9H), 2.53-2.64 (m, 2H), 3.04-3.13 (m, 2H), 3.22 (t, J = 6.3 Hz, 2H), 4.09 (d, J = 4.6 Hz, 2H), 5.91 (br. s, 1H), 7.08 (br. s., 1H), 7.32 (d, J= 9.0 Hz, 1H), 7.38 (s, 1H), 8.43 (d, J = 9.0 Hz, 1H).

[0302] 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]amino]methyl]piperidine: 310 mg, 40%; ESI/MS m/e 427.3 (M⁺+H, C₂₀H₂₈F₂N₄O₄).

[0303] 4-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]methyl]piperidine: 1.35 g, 57%; ESI/MS m/e 459.3 (M⁺+H, C₂₁H₂₉F₃N₄O₄).

[Example 1736] Synthesis of 4-[[N-(2-amino-5-chlorobenzoyl)glycyl]aminomethyl]-1-(4-ethoxybenzyl)piperidine (Compd. No. 1429) and 1-(4-ethoxybenzyl)-4-[[N-(2-(4-ethoxybenzyl)amino-5-chlorobenzoyl)glycyl]aminomethyl]piperidine (Compd. No. 1433)

[0304] A methanol (0.4 mL) solution of sodium cyanoborohydride (140 mmol) was added to a mixture of 4-[[N-(2-amino-5-chlorobenzoyl)glycyl]aminomethyl]piperidine (0.10 mmol) with 4-ethoxybenzaldehyde (0.10 mmol), acetic acid (0.050 mL) and methanol (1.6 mL), and the resulting mixture was stirred at 60 °C for 14 hours. The obtained reaction mixture was loaded onto a Varian™ SCX column and washed with methanol (20 mL). The resulting products were eluted with a 2 M methanol solution of NH₃, concentrated and purified by preparative TLC (SiO₂, ethyl acetate/methanol) to thereby provide 4-[[N-(2-amino-5-chlorobenzoyl)glycyl]aminomethyl]-1-(4-ethoxybenzyl)piperidine (Compd. No. 1429) and 1-(4-ethoxybenzyl)-4-[[N-(2-(4-ethoxybenzyl)amino-5-chlorobenzoyl)glycyl]aminomethyl]piperidine (Compd. No. 1433).

[0305] Compd. No. 1429: 4.5 mg; 20%. The purity was determined by RPLC/MS (95%). ESI/MS m/e 459.2 (M⁺+H, C₂₄H₃₁ClN₄O₃).

[0306] Compd. No. 1433: 8.4 mg, 28%. The purity was determined by RPLC/MS (98%). ESI/MS m/e 593.2 (M⁺+H, C₃₃H₄₁ClN₄O₄).

[Examples 1737 to 1779]

[0307] The compounds used in the present invention were synthesized by using respective starting materials and reactants according to the method of Example 1736. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 36.

Table 36

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1737	1430	C ₂₄ H ₂₉ ClN ₄ O ₄	473.0	3.1	13
1738	1431	C ₂₄ H ₃₁ BrN ₄ O ₃	505.2	5.8	23
1739	1432	C ₂₄ H ₂₉ BrN ₄ O ₄	517.0	4.1	16
1740	1434	C ₃₃ H ₄₁ BrN ₄ O ₆	637.2	9.7	30
1741	1435	C ₂₄ H ₃₁ ClN ₄ O ₂	443.2	9.7	44
1742	1436	C ₂₅ H ₃₃ ClN ₄ O ₂	457.2	12.5	55
1743	1437	C ₂₅ H ₃₃ ClN ₄ O ₃	473.2	9.4	40
1744	1438	C ₂₄ H ₃₁ BrN ₄ O ₂	489.2	5.9	24

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Table 36 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	1745	C ₂₅ H ₃₃ BrN ₄ O ₂	503.2	15.2	61
	1746	C ₂₅ H ₃₃ BrN ₄ O ₃	519.2	11.0	43
	1747	C ₂₃ H ₂₉ BrN ₄ O ₂ S	507.2	9.3	37
10	1748	C ₃₃ H ₄₁ CIN ₄ O ₂	561.4	6.8	24
	1749	C ₃₅ H ₄₅ CIN ₄ O ₂	589.4	9.8	33
	1750	C ₃₅ H ₄₅ CIN ₄ O ₄	621.4	9.4	30
15	1751	C ₃₃ H ₄₁ BrN ₄ O ₂	605.2	6.5	21
	1752	C ₃₅ H ₄₅ BrN ₄ O ₂	635.2	10.7	34
	1753	C ₃₅ H ₄₅ BrN ₄ O ₄	665.4	12.4	37
20	1754	C ₃₁ H ₃₇ BrN ₄ O ₂ S ₂	643.2	7.6	24
	1755	C ₂₄ H ₃₂ CIN ₅ O ₂	458.2	4.5	20
	1756	C ₂₃ H ₂₉ CIN ₄ O ₄	461.2	6.0	26
25	1757	C ₂₄ H ₃₂ BrN ₅ O ₂	504.0	6.8	27
	1758	C ₂₃ H ₂₉ BrN ₄ O ₄	505.0	8.0	32
	1759	C ₃₁ H ₃₇ CIN ₄ O ₆	597.2	5.9	20
30	1760	C ₃₁ H ₃₇ BrN ₄ O ₆	643.2	6.0	19
	1761	C ₂₆ H ₃₆ CIN ₅ O ₂	486.2	5.5	23
	1762	C ₂₃ H ₂₉ CIN ₄ O ₄	463.0	5.8	25
35	1763	C ₂₆ H ₃₆ BrN ₅ O ₂	530.2	4.2	16
	1764	C ₂₃ H ₂₉ BrN ₄ O ₄	505.0	6.5	26
	1765	C ₃₁ H ₃₇ CIN ₄ O ₆	597.2	4.3	14
40	1766	C ₃₁ H ₃₇ BrN ₄ O ₆	641.2	5.3	17
	1767	C ₂₃ H ₂₉ CIN ₄ O ₂ S	461.0	2.7	12
	1768	C ₃₁ H ₃₇ CIN ₄ O ₂ S ₂	597.2	4.9	16
45	1769	C ₃₇ H ₄₉ BrN ₄ O ₂	663.2	5.5	17
	1770	C ₂₆ H ₃₅ BrN ₄ O ₂	515.2	6.0	23
	1771	C ₃₅ H ₄₅ BrN ₄ O ₂	633.2	5.0	16
50	1772	C ₂₅ H ₃₃ BrN ₄ O ₂	501.0	6.2	25
	1773	C ₃₇ H ₄₉ CIN ₄ O ₂	617.4	5.6	18
	1774	C ₂₆ H ₃₅ CIN ₄ O ₂	471.2	5.9	25
55	1775	C ₃₅ H ₄₅ CIN ₄ O ₂	589.2	4.6	16
	1776	C ₂₅ H ₃₃ CIN ₄ O ₂	457.2	5.3	23
	1777	C ₂₆ H ₃₃ F ₃ N ₄ O ₂	491.2	4.7	12.8
	1778	C ₂₅ H ₂₉ F ₃ N ₄ O ₃	491.2	3.7	10.1
	1779	C ₂₆ H ₃₂ F ₂ N ₄ O ₂	459.2	3.3	9.6

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[Example 1780] Synthesis of 4-[[N-(2-amino-5-trifluoromethoxybenzoyl)glycyl]aminomethyl]-1-(4-isopropylbenzyl) piperidine (Compd. No. 1903)

[0308] Acetic acid (10 mL) was added to a mixture of 4-[[N-(2-(tert-butoxycarbonylamino)-5-(trifluoromethoxy)benzoyl)glycyl]aminomethyl]piperidine (0.050 mmol) with 4-isopropylbenzaldehyde (0.060 mmol), NaH₃CN (0.15 mmol) and methanol (1.3 mL), and the resulting mixture was stirred at 60 °C for 8 hours, cooled to room temperature, then loaded onto a Varian™ SCX column and washed with methanol (10 mL). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. A 4 M dioxane solution of HCl (2 mL) was then added to the resulting residue, and the obtained solution was stirred at room temperature overnight, concentrated and then purified by preparative TLC to provide 4-[[N-(2-amino-5-trifluoromethoxybenzoyl)glycyl]aminomethyl]-1-(4-isopropylbenzyl) piperidine (Compd. No. 1903) (6.6 mg, 26%). The purity was determined by RPLC/MS (93%). ESI/MS m/e 507 (M⁺+H, C₂₆H₃₃F₃N₄O₃).

[Examples 1781 to 1783]

[0309] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1780. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 37.

Table 37

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1781	1904	C ₂₆ H ₃₃ F ₃ N ₄ O ₃	507	9.6	37.9
1782	1917	C ₂₅ H ₃₁ F ₃ N ₄ O ₅	525.2	1.2	3.1
1783	1918	C ₂₄ H ₂₉ F ₃ N ₄ O ₄	495.2	2.8	7.5

[Example 1784] Synthesis of 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(5-bromo-2-ethoxybenzyl) piperidine (Compd. No. 2052)

[0310] NaBH₃CN (0.25 mmol) was added to a mixture of 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (0.050 mmol) with 5-bromo-2-ethoxybenzaldehyde (0.15 mmol), methanol (1.2 mL) and acetic acid (0.030 mL). The resulting mixture was stirred at 50 °C for 13 hours, cooled to room temperature, loaded onto a Varian™ SCX column and washed with methanol (5 mL × 3). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. Dichloromethane (1 mL) and trifluoroacetic acid (0.50 mL) were added to the resulting residue, and the mixture was stirred at room temperature for 10 minutes. The reaction mixture was concentrated, and the residue was dissolved in methanol. The resulting solution was loaded onto a Varian™ SCX column and washed with methanol (5 mL). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL), concentrated and purified by preparative TLC (SiO₂, ethyl acetate/methanol = 10:1) to provide 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(5-bromo-2-ethoxybenzyl)piperidine (Compd. No. 2052) (10.2 mg, 38%). The purity was determined by RPLC/MS (96%). ESI/MS m/e 539.2 (M⁺+H, C₂₄H₂₉BrF₂N₄O₃).

[Examples 1785 to 1792]

[0311] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1784. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 38.

Table 38

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1785	2053	C ₃₀ H ₃₄ F ₂ N ₄ O ₄	553.4	12.7	46
1786	2054	C ₂₇ H ₃₀ F ₂ N ₄ O ₃	497.2	13.7	55
1787	2055	C ₂₃ H ₂₈ F ₂ N ₄ O ₄	463.2	10.1	44
1788	2056	C ₂₂ H ₂₄ BrF ₃ N ₄ O ₂	515.2	7.7	30
1789	2057	C ₂₃ H ₂₇ BrF ₂ N ₄ O ₃	527.0	8.6	33

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Table 38 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1790	2058	C ₂₄ H ₃₀ F ₂ N ₄ O ₄	477.2	6.4	27
1791	2059	C ₂₈ H ₃₀ F ₂ N ₄ O ₃	509.4	6.7	26
1792	2060	C ₂₅ H ₃₂ F ₂ N ₄ O ₅	507.2	7.2	28

[Example 1793] Synthesis of 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(3,4-diethoxybenzyl)piperidine (Compd. No. 2065)

[0312] NaBH₃CN (0.25 mmol) was added to a mixture of 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (0.050 mmol) with 3,4-diethoxybenzaldehyde (0.15 mol), methanol (1.2 mL) and acetic acid (0.050 mL), and the obtained mixture was stirred at 50 °C overnight, cooled to room temperature, loaded onto a Varian™ SCX column and washed with methanol (5 mL×2). The obtained product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. Dichloromethane (2 mL) and phenyl isocyanate (0.10 mL) were added to the obtained residue, and the resulting mixture was stirred at room temperature for 1 hour, loaded onto a Varian™ SCX column and washed with methanol (5 mL). The obtained product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. The residue was dissolved in methanol (0.25 mL), and a 4 M dioxane solution of HCl (0.125 mL) was added to the resulting solution. The obtained mixture was stirred at room temperature overnight and concentrated. The resulting residue was dissolved in methanol, loaded onto a Varian™ SCX column and washed with methanol (5 mL×2). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated to thereby afford 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(3,4-diethoxybenzyl)piperidine (Compd. No. 2065) (21.2 mg, 84%). The purity was determined by RPLC/MS (97%). ESI/MS m/e 505.2 (M⁺+H, C₂₆H₃₄F₂N₄O₄).

[Examples 1794 to 1808]

[0313] The compounds used in the present invention were synthesized by using the respective corresponding raw materials and reactants according to the method of Example 1793. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 39.

Table 39

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1794	2061	C ₂₃ H ₂₇ F ₃ N ₄ O ₂	449.2	12.6	56
1795	2062	C ₂₃ H ₂₇ F ₃ N ₄ O ₃	465.2	19.7	85
1796	2063	C ₂₅ H ₃₂ F ₂ N ₄ O ₄	491.2	19.8	81
1797	2064	C ₂₂ H ₂₄ BrF ₃ N ₄ O ₂	515.2	17.5	68
1798	2066	C ₂₉ H ₃₂ F ₂ N ₄ O ₃	523.2	18.0	69
1799	2067	C ₂₆ H ₃₄ F ₂ N ₄ O ₂	473.2	21.9	93
1800	2068	C ₂₂ H ₂₄ ClF ₃ N ₄ O ₂	469.2	11.2	48
1801	2069	C ₂₄ H ₃₀ F ₂ N ₄ O ₃	461.4	20.2	88
1802	2070	C ₂₃ H ₂₇ BrF ₂ N ₄ O ₃	527.2	17.7	67
1803	2071	C ₂₄ H ₃₀ F ₂ N ₄ O ₄	477.2	10.9	46
1804	2072	C ₂₅ H ₃₂ F ₂ N ₄ O ₃	475.2	19.3	81
1805	2073	C ₂₉ H ₃₂ F ₂ N ₄ O ₃	523.2	22.8	87
1806	2074	C ₂₉ H ₃₂ F ₂ N ₄ O ₄	539.2	22.5	84
1807	2075	C ₂₃ H ₂₇ F ₃ N ₄ O ₃	465.2	14.9	64
1808	2076	C ₂₂ H ₂₄ F ₄ N ₄ O ₂	453.2	21.9	97

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[Example 1809] Synthesis of 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(2-hydroxy-3-methylbenzyl)piperidine (Compd. No. 2106)

[0314] NaBH₃CN (0.40 mmol) was added to a mixture of 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (0.050 mmol) with 2-hydroxy-3-methylbenzaldehyde (0.25 mmol), methanol (1.0 mL) and acetic acid (0.040 mL). The resulting mixture was stirred at 50 °C overnight, cooled to room temperature, loaded onto a Varian™ SCX column and washed with methanol (5 mL×2). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. The residue was dissolved in ethyl acetate/methanol = 5:1 (1 mL), loaded onto a Varian™ SCX column, eluted with ethyl acetate/methanol = 5:1 (5 mL) and concentrated. The residue was dissolved in methanol (2 mL), and a 4 M dioxane solution of HCl (0.50 mL) was added to the resulting solution. The obtained mixture was stirred at room temperature overnight and concentrated. The residue was dissolved in methanol, loaded onto a Varian™ SCX column and washed with methanol (5 mL×2). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL), concentrated and purified by preparative TLC to thereby provide 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(2-hydroxy-3-methylbenzyl)piperidine (Compd. No. 2106). The purity was determined by RPLC/MS (97%). ESI/MS m/e 447.0 (M⁺+H, C₂₃H₂₈F₂N₄O₃).

[Examples 1810 to 1823]

[0315] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1809. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 40.

Table 40

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1810	2077	C ₂₂ H ₂₅ ClF ₂ N ₄ O ₃	467.2	3.7	16
1811	2078	C ₂₄ H ₃₀ F ₂ N ₄ O ₄	477.2	1.9	8
1812	2079	C ₃₀ H ₃₄ F ₂ N ₄ O ₄	553.4	4.8	17
1813	2080	C ₂₂ H ₂₅ ClF ₂ N ₄ O ₃	467.2	13.5	58
1814	2081	C ₂₂ H ₂₅ ClF ₂ N ₄ O ₃	467.2	13.8	59
1815	2082	C ₂₃ H ₂₈ F ₂ N ₄ O ₄	463.2	9.6	42
1816	2105	C ₂₃ H ₂₈ F ₂ N ₄ O ₄	463.2	ND	ND
1817	2106	C ₂₃ H ₂₈ F ₂ N ₄ O ₃	447.0	ND	ND
1818	2107	C ₂₀ H ₂₃ BrF ₂ N ₄ O ₂ S	503.1	ND	ND
1819	2108	C ₂₅ H ₂₈ F ₂ N ₄ O ₂ S	487.2	ND	ND
1820	2109	C ₂₀ H ₂₃ BrF ₂ N ₄ O ₃	487.0	ND	ND
1821	2110	C ₂₂ H ₂₈ F ₂ N ₄ O ₃	435.1	ND	ND
1822	2111	C ₂₂ H ₂₄ ClF ₃ N ₄ O ₂	469.0	ND	ND
1823	2112	C ₂₄ H ₂₉ BrF ₂ N ₄ O ₄	557.0	ND	ND
Note: ND means "Not Determined".					

[Example 1824] Synthesis of 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(3-amino-4-methylbenzyl)piperidine (Compd. No. 2114)

[0316] NaBH₃CN (0.50 mmol) was added to a mixture of 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (0.050 mmol) with 4-methyl-3-nitrobenzaldehyde (0.25 mmol), methanol (1.2 mL) and acetic acid (0.050 mL). The resulting mixture was stirred at 50 °C overnight, cooled to room temperature, loaded onto a Varian™ SCX column and washed with methanol (5 mL×2). The obtained product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. The residue was dissolved in ethyl acetate/methanol = 2:1 (2 mL), loaded onto a Varian™ Si column, eluted with ethyl acetate/methanol = 2:1 (6 mL) and concentrated. The obtained residue was dissolved in methanol (1 mL), and a 4 M dioxane solution of HCl (0.50 mL) was added to the resulting solution. The obtained mixture was stirred at room temperature overnight and concentrated. The resulting residue was dissolved

in methanol, loaded onto a Varian™ SCX column, washed with methanol (5 mL×2), then eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated to thereby afford 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(4-methyl-3-nitrobenzyl)piperidine.

[0317] A mixture of the resulting 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(4-methyl-3-nitrobenzyl)piperidine with a 5% palladium carbon (15 mg) and methanol (2 mL) was stirred at room temperature under a hydrogen atmosphere for 4 hours. The palladium catalyst was removed by filtration through Celite, and the filtrate was concentrated and purified by preparative TLC (SiO₂, ethyl acetate/methanol = 3:1) to thereby provide 4-[[N-(2-amino-4, 5-difluorobenzoyl)glycyl]aminomethyl]-1-(3-amino-4-methylbenzyl)piperidine (Compd. No. 2114) (2.9 mg, 13%). The purity was determined by RPLC/MS (100%). ESI/MS m/e 446.1 (M⁺+H, C₂₃H₂₉F₂N₅O₂).

[Example 1825] Synthesis of 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(3-amino-4-methoxybenzyl)piperidine (Compd. No. 2113)

[0318] The title compound 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(3-amino-4-methoxybenzyl)piperidine (Compd. No. 2113) was synthesized by using the corresponding starting material and reactants according to the method of Example 1824. 4.6 mg, 20% yield; ESI/MS m/e 462.2 (M⁺+H, C₂₃H₂₉F₂N₅O₃).

[Example 1826] Synthesis of 1-(3-amino-4-hydroxybenzyl)-4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine

[0319] A methanol (3.2 mL) solution of NaBH₃CN (1.58 mmol) was added to a mixture of 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (0.35 mmol) with 4-hydroxy-3-nitrobenzaldehyde (1.22 mmol), methanol (3.8 mL) and acetic acid (0.175 mL), and the resulting mixture was stirred at 50 °C overnight, cooled to room temperature, loaded onto a Varian™ SCX column and washed with methanol (5 mL×2). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. The residue was dissolved in ethyl acetate/methanol = 5:1, loaded onto a Varian™ Si column, eluted with ethyl acetate/methanol = 5:1 (10 mL) and concentrated to thereby afford 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(4-hydroxy-3-nitrobenzyl)piperidine (175 mg, 87%).

[0320] A mixture of the resulting 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(4-hydroxy-3-nitrobenzyl)piperidine with a 10% palladium carbon (45 mg) and methanol (5 mL) was stirred at room temperature under a hydrogen atmosphere for 4 hours. The palladium catalyst was removed by filtration, and the filtrate was concentrated to provide 1-(3-amino-4-hydroxybenzyl)-4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (100 mg, 60%).

[Example 1827] Synthesis of 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(3-amino-4-hydroxybenzyl)piperidine (Compd. No. 2141)

[0321] A 4 M dioxane solution of HCl (0.50 mL) was added to a methanol (1 mL) solution of 1-(3-amino-4-hydroxybenzyl)-4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (20.0 mg, 0.035 mmol), and the resulting mixture was stirred at room temperature overnight and concentrated. The obtained residue was then dissolved in methanol, loaded onto a Varian™ SCX column, washed with methanol (5 mL×2), eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated to thereby afford 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(3-amino-4-hydroxybenzyl)piperidine (Compd. No. 2141) (17.6 mg, quantitative). The purity was determined by RPLC/MS (85%). ESI/MS m/e 448.3 (M⁺+H, C₂₂H₂₇F₂N₅O₃).

[Examples 1828 to 1831]

[0322] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the methods of Examples 1826 and 1827. The obtained products, if necessary, were purified by preparative TLC to provide the objective compounds. Data of ESI/MS and yields (mg) and yields (%) in the final steps are collectively shown in Table 41.

Table 41

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1828	2140	C ₂₃ H ₂₇ F ₂ N ₅ O ₄	476.3	6.7	28.4
1829	2144	C ₂₄ H ₃₀ F ₃ N ₅ O ₃	494.2	18.7	82.0

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Table 41 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1830	2145	C ₂₃ H ₂₈ F ₃ N ₅ O ₃	480.3	19.8	63.7
1831	2146	C ₂₄ H ₂₈ F ₃ N ₅ O ₄	508.3	13.5	81.7

[Example 1832] Synthesis of 1-(3-amino-4-chlorobenzyl)-4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine

[0323] A methanol (1.3 mL) solution of NaBH₃CN (0.63 mmol) was added to a mixture of 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (0.14 mmol) with 4-chloro-3-nitrobenzaldehyde (0.50 mmol), methanol (1.5 mL) and acetic acid (0.070 mL). The resulting mixture was stirred at 50 °C overnight, cooled to room temperature, loaded onto a Varian™ SCX column and washed with methanol. The obtained product was eluted with a 2 M methanol solution of NH₃ and concentrated. The residue was dissolved in ethyl acetate/methanol = 5:1, loaded onto a Varian™ Si column, eluted with ethyl acetate/methanol = 5:1 (6 mL) and concentrated to thereby provide 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(4-chloro-3-nitrobenzyl)piperidine (44 mg, 53%). ESI/MS m/e 596.3 (M⁺+H).

[0324] A mixture of 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(4-chloro-3-nitrobenzyl)piperidine (121 mg, 0.20 mmol) with a 10% palladium carbon (85 mg), ethyl acetate (10 mL) and methanol (1 mL) was stirred at room temperature under a hydrogen atmosphere for 19 hours. The palladium catalyst was removed by filtration, and the filtrate was concentrated to thereby afford 1-(3-amino-4-chlorobenzyl)-4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (78 mg, 68%).

[Example 1833] Synthesis of 1-(3-amino-4-chlorobenzyl)-4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (Compd No. 2142)

[0325] The title compound 1-(3-amino-4-chlorobenzyl)-4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (Compd. No. 2142) was synthesized by using the corresponding starting material and reactants according to the method of Example 1827. 13.7 mg, 98%. The purity was determined by RPLC/MS (83%). ESI/MS m/e 466.2 (M⁺+H, C₂₂H₂₆ClF₂N₅O₂).

[Example 1834] Synthesis of 1-(3-acetylamino-4-hydroxybenzyl)-4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (Compd. No. 2148)

[0326] A dichloromethane (0.12 mL) solution of acetic anhydride (0.12 mmol) was added to a mixture of 1-(3-amino-4-hydroxybenzyl)-4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (27 mg, 0.049 mmol) with a (piperidinomethyl)polystyrene (2.7 mmol/g, 60 mg, 0.15 mmol) and dichloromethane (2 mL), and the resulting mixture was stirred at room temperature for 3 hours. The mixture was loaded onto a Varian™ SCX column and washed with methanol. The obtained crude product was eluted with a 2 M methanol solution of NH₃ and concentrated. The residue was dissolved in ethyl acetate/methanol = 5:1, loaded onto a Varian™ Si column, eluted with ethyl acetate/methanol = 5:1 (6 mL) and concentrated to thereby provide 1-(3-acetylamino-4-hydroxybenzyl)-4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (30 mg, quantitative). ESI/MS m/e 590.4 (M⁺+H, C₂₉H₃₇N₅O₆).

[0327] A 4 M dioxane solution of HCl (0.50 mL) was added to a methanol (1 mL) solution of the 1-(3-acetylamino-4-hydroxybenzyl)-4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine obtained above, and the resulting solution was stirred at room temperature overnight and concentrated. The resulting residue was then dissolved in methanol, loaded onto a Varian™ SCX column, washed with methanol (5 mL ×2), eluted with a 2 M methanol solution of NH₃ (5 mL), concentrated and then purified by preparative TLC (SiO₂, ethyl acetate/methanol = 3:2) to thereby afford 1-(3-acetylamino-4-hydroxybenzyl)-4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (Compd. No. 2148) (2.3 mg, 9.2%). The purity was determined by RPLC/MS (98%). ESI/MS m/e 490.3 (M⁺+H, C₂₄H₂₉F₂N₅O₄).

[Examples 1835 to 1839]

[0328] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the methods of Examples 1826 and 1834. Data of ESI/MS and yields (mg) and yields (%) in the final steps are collectively shown in Table 42.

Table 42

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1835	2143	C ₂₅ H ₂₉ F ₂ N ₅ O ₅	518.3	4.8	45
1836	2147	C ₂₅ H ₃₁ F ₂ N ₅ O ₄	504.3	3.0	23
1837	2154	C ₂₆ H ₃₂ F ₃ N ₅ O ₄	536.4	4.1	66
1838	2155	C ₂₆ H ₃₀ F ₃ N ₅ O ₄	522.3	5.5	71
1839	2156	C ₂₆ H ₃₀ F ₃ N ₅ O ₅	550.3	7.0	78

[Example 1840] Synthesis of 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(3-methylamino-4-hydroxybenzyl)piperidine (Compd. No. 2160)

[0329] A methanol (0.2 mL) solution of NaBH₃CN (7.0 mg) was added to a mixture of 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(3-amino-4-hydroxy)piperidine (20.4 mg, 0.037 mmol) with a 37% HCHO solution (3.0 mg, 0.037 mmol), acetic acid (0.1 mL) and methanol (1.3 mL), and the resulting mixture was stirred at 60 °C overnight, cooled to room temperature, loaded onto a Varian™ SCX column and washed with methanol (5 mL×2). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (8 mL) and concentrated to thereby provide 4-[[N-(2-tert-butoxycarbonylamino)-4,5-difluorobenzoyl]glycyl]aminomethyl]-1-(3-methylamino-4-hydroxybenzyl)piperidine.

[0330] A 4 M dioxane solution of HCl (1.0 mL) was added to a methanol (1.0 mL) solution of the 4-[[N-(2-tert-butoxycarbonylamino)-4,5-difluorobenzoyl]glycyl]aminomethyl]-1-(3-methylamino-4-hydroxybenzyl)piperidine obtained above, and the resulting mixture was stirred at room temperature for 3 hours and concentrated. The obtained residue was then dissolved in methanol (1 mL), loaded onto a Varian™ SCX column, washed with methanol (5 mL×2), eluted with a 2 M methanol solution of NH₃ (8 mL), concentrated and then purified by preparative TLC (SiO₂) to thereby afford 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(3-methylamino-4-hydroxybenzyl)piperidine (Compd. No. 2160) (3.4 g, 20%). The purity was determined by RPLC/MS (96%). ESI/MS m/e 462.4 (M⁺+H, C₂₃H₂₉F₂N₅O₃).

[Examples 1841 to 1844]

[0331] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the methods of Examples 1826 and 1840. Data of ESI/MS and yields (mg) and yields (%) in the final steps are collectively shown in Table 43.

Table 43

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1841	2159	C ₂₄ H ₃₁ F ₂ N ₅ O ₃	476.3	7.6	48
1842	2161	C ₂₃ H ₂₈ ClF ₂ N ₅ O ₂	480.3	7.3	45
1843	2162	C ₂₅ H ₃₂ F ₃ N ₅ O ₃	508.4	6.0	24
1844	2163	C ₂₄ H ₃₀ F ₃ N ₅ O ₃	494.3	4.3	15

[Example 1845] Synthesis of 4-[[N-(2-amino-4, 5-difluorobenzoyl)glycyl]aminomethyl]-1-(benzo[c]furazan-5-yl)piperidine (Compd. No. 2130)

[0332] A mixture of 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (0.050 mmol) with 5-(bromomethyl)benzo[c]furazan (0.75 mL), a (piperidinomethyl)polystyrene (2.6-2.8 mmol/g, 60 mg, 0.15 mmol), methanol (0.2 mL), acetonitrile (1.0 mL) and chloroform (0.50 mL) was stirred at 50 °C overnight, cooled to room temperature, loaded onto a Varian™ SCX column and washed with methanol (5 mL×2). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. Chloroform (1.5 mL) and phenyl isocyanate (0.075 mL) were added to the residue, and the resulting mixture was stirred at room temperature for 1 hour, loaded onto a Varian™ SCX column and washed with methanol (5 mL×2). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. The resulting residue was dissolved in methanol (1 mL), and a 4 M dioxane solution of HCl (0.50 mL) was added to the obtained solution. The resulting mixture was stirred at room temperature overnight and concentrated. The residue was then dissolved in methanol, loaded onto a Varian™

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SCX column, washed with methanol (5 mL ×2), eluted with a 2 M methanol solution of NH₃ (5 mL), concentrated and then purified by preparative TLC (SiO₂, ethyl acetate/methanol = 5:1) to provide 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(benzo[c]furazan-5-yl)piperidine (Compd. No. 2130) (3.6 mg, 16%). The purity was determined by RPLC/MS (87%). ESI/MS m/e 459.3 (M⁺+H, C₂₂H₂₄F₂N₆O₃).

[Example 1846] Synthesis of 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(3,5-dimethylisoxazol-4-yl)piperidine (Compd. No. 2131)

[0333] The title compound 4-[[N-(2-amino-4, 5-difluorobenzoyl)glycyl]aminomethyl]-1-(3,5-dimethylisoxazol-4-yl)piperidine (Compd. No. 2131) was synthesized by using the corresponding starting material and reactants according to the method of Example 1845. 3.8 mg, 18% yield; ESI/MS m/e 436.2 (M⁺+H, C₂₁H₂₇F₂N₅O₃).

[Example 1847] Synthesis of 4-[[N-(2-amino-5-chlorobenzoyl)glycyl]aminomethyl]-1-[4-(trifluoromethylthio)benzyl]piperidine (Compd. No. 1616)

[0334] A mixture of 4-[[N-(2-amino-5-chlorobenzoyl)glycyl]aminomethyl]piperidine (16.2 mg, 0.050 mmol) with 4-(trifluoromethylthio)benzyl chloride (20.3 mg, 0.075 mmol), acetonitrile (1.0 mL) and chloroform (0.50 mL) was stirred at 60 °C for 15 hours, cooled, then loaded onto a Varian™ SCX column and washed with methanol (15 mL). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated to thereby afford 4-[[N-(2-amino-5-chlorobenzoyl)glycyl]aminomethyl]-1-[4-(trifluoromethylthio)benzyl]piperidine (Compd. No. 1616) (21.9 mg, 85%). The purity was determined by RPLC/MS (96%). ESI/MS m/e 545.2 (M⁺+H, C₂₃H₂₆ClF₃N₄O₂S).

[Examples 1848 to 1868]

[0335] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1847. The obtained products, if necessary, were purified by preparative TLC to provide the objective compounds. Data of ESI/MS and yields (mg) and yields (%) in the final steps are collectively shown in Table 44.

Table 44

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1848	1617	C ₂₃ H ₂₆ BrF ₃ N ₄ O ₂ S	559.0	21.0	75
1849	1777	C ₂₃ H ₂₅ Cl ₂ F ₃ N ₄ O ₂	517.0	16.3	63.0
1850	1778	C ₂₄ H ₂₉ F ₃ N ₄ O ₂	463.2	9.5	41.1
1851	1779	C ₂₄ H ₂₇ F ₃ N ₄ O ₄	493.2	12.7	51.6
1852	1780	C ₂₃ H ₂₆ BrF ₃ N ₄ O ₂	527.0	16.4	62.2
1853	1781	C ₂₃ H ₂₇ F ₃ N ₄ O ₃	465.2	10.0	28.7
1854	1782	C ₂₅ H ₂₉ F ₃ N ₄ O ₂	475.2	12.2	34.3
1855	1783	C ₂₄ H ₂₆ F ₃ N ₅ O ₂	474.2	17.2	48.4
1856	1784	C ₂₃ H ₂₇ F ₃ N ₄ O ₂	449.2	11.3	33.6
1857	1788	C ₂₅ H ₃₁ F ₃ N ₄ O ₂	477.2	10.0	42.0
1858	1789	C ₂₄ H ₂₉ F ₃ N ₄ O ₃	479.2	10.0	27.9
1859	1792	C ₂₄ H ₃₀ F ₂ N ₄ O ₂	445.2	5.9	26.5
1860	1793	C ₂₂ H ₂₄ Cl ₂ F ₂ N ₄ O ₂	485.2	9.2	37.9
1861	1794	C ₂₃ H ₂₈ F ₂ N ₄ O ₂	431.2	5.7	26.5
1862	1795	C ₂₃ H ₂₆ F ₂ N ₄ O ₄	461.2	6.0	26.1
1863	1796	C ₂₂ H ₂₅ BrF ₂ N ₄ O ₂	497.0	10.5	42.4
1864	1797	C ₂₂ H ₂₆ F ₂ N ₄ O ₃	433.2	3.5	16.2
1865	1798	C ₂₃ H ₂₈ F ₂ N ₄ O ₃	447.2	5.6	25.1

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Table 44 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1866	1799	C ₂₄ H ₂₈ F ₂ N ₄ O ₂	443.2	5.5	24.9
1867	1800	C ₂₃ H ₂₅ F ₂ N ₅ O ₂	442.2	9.4	42.6
1868	1801	C ₂₂ H ₂₆ F ₂ N ₄ O ₂	417.2	6.5	31.2

[Example 1869] Synthesis of 4-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]aminomethyl]-1-(4-bromobenzyl)piperidine (Compd. No. 1910)

[0336] A mixture of 4-[[N-(2-tert-butoxycarbonylamino)-5-trifluoromethoxybenzoyl]glycyl]aminomethyl]piperidine (0.050 mmol) with 4-bromobenzyl bromide (0.060 mmol), a piperidinomethylpolystyrene (60mg), acetonitrile (0.8 mL) and chloroform (0.5 mL) was stirred at 60 °C for 12 hours, cooled, then loaded onto a Varian™ SCX column and washed with a 50% chloroform/methanol (10 mL) and methanol (10 mL). The obtained product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. A 4 M 1, 4-dioxane solution of HCl (2 mL) was added to the resulting residue, and the obtained mixture was stirred at room temperature overnight, concentrated and then purified by preparative TLC to thereby provide 4-[[N-(2-amino-5-trifluoromethoxybenzoyl)glycyl]aminomethyl]-1-(4-bromobenzyl)piperidine (Compd. No. 1910) (6.5 mg, 24%). The purity was determined by RPLC/MS (96%). ESI/MS m/e 545 (M⁺+H, C₂₃H₂₆BrF₃N₄O₃).

[Examples 1870 to 1873]

[0337] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1869. Data of ESI/MS and yields (mg) and yields (%) in the final steps are collectively shown in Table 45.

Table 45

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1870	1911	C ₂₃ H ₂₅ Cl ₂ F ₃ N ₄ O ₃	533	10.6	39.7
1871	1912	C ₂₃ H ₂₇ F ₃ N ₄ O ₄	481	12.5	52.0
1872	1913	C ₂₅ H ₃₁ F ₃ N ₄ O ₃	493	7.5	30.5
1873	1914	C ₂₄ H ₂₉ F ₃ N ₄ O ₃	479	11.0	46.0

[Example 1874] Synthesis of 4-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]aminomethyl]-1-(benz[d]imidazol-5-yl)piperidine (Compd. No. 2186)

[0338] A mixture of 4-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]aminomethyl]piperidine (0.060 mmol) with 1-(tert-butoxycarbonyl)-6-(bromomethyl)benz[d]imidazole (15.6 mg, 0.050 mmol), a (piperidinomethyl)polystyrene (86 mg, 0.15 mmol) and acetonitrile (2 mL) was stirred at 50 °C for 3 hours and cooled to room temperature. Phenyl isocyanate (30 mg) was then added to the cooled mixture, and the resulting mixture was stirred at room temperature for 1 hour, loaded onto a Varian™ SCX column and washed with methanol (5 mL) and chloroform (5 mL). The obtained product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated.

[0339] The resulting substance was dissolved in methanol (1 mL), and a 4 M dioxane solution of HCl (1 mL) was added to the obtained solution. The resulting mixture was stirred at room temperature overnight, loaded onto a Varian™ SCX column, washed with methanol (5 mL) and dichloromethane. The resulting product was eluted with a 2 M methanol solution of NH₃ and concentrated. The obtained crude product was purified by preparative TLC (SiO₂, ethyl acetate/methanol = 3:1) to thereby afford 4-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]aminomethyl]-1-(benz[d]imidazol-5-yl)piperidine (Compd. No. 2186) (1.9 mg, 7.8%). The purity was determined by RPLC/MS (100%). ESI/MS m/e 489.4 (M⁺+H, C₂₄H₂₇F₃N₆O₂).

[Example 1875] Synthesis of 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(benzo[c]thiadiazol-5-yl)piperidine (Comnd. No. 2184)

[0340] Methanesulfonyl chloride (0.0042 mL) was added to a mixture of 5-(hydroxymethyl)benzo[c]thiadiazole (8.3

mg, 0.050 mmol) with a (piperidinomethyl)polystyrene (86 mg) and chloroform (1 mL), and the resulting mixture was stirred at room temperature for 1.5 hours. Acetonitrile (1 mL) and 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine were added to the mixture, and the resulting reaction mixture was stirred at 50 °C for 3 hours and cooled to room temperature. Phenyl isocyanate (30 mg) was then added to the cooled mixture, and the resulting mixture was stirred at room temperature for 1 hour, loaded onto a Varian™ SCX column and washed with methanol (5 mL) and chloroform (5 mL). The product was eluted with a 2 M methanol solution of NH₃ (3 mL) and concentrated. The resulting residue was dissolved in dichloromethane (1 mL), and a dichloromethane (1 mL) solution of chlorotrimethylsilane (1 M) and phenol (1 M) was added to the obtained solution. The resulting mixture was stirred at room temperature for 5 hours, then loaded onto a Varian™ SCX column and washed with methanol and dichloromethane. The obtained crude product was eluted with a 2 M methanol solution of NH₃ and purified by preparative TLC (SiO₂, ethyl acetate/methanol = 3:1) to thereby provide 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(benzo[c]thiadiazol-5-yl)piperidine (Compd. No. 2184) (1.3 mg, 5.5%). The purity was determined by RPLC/MS (100%). ESI/MS m/e 475.2 (M⁺+H, C₂₂H₂₄F₂N₆O₂S).

[Example 1876] Synthesis of 4-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]aminomethyl]-1-(benzo[c]thiadiazol-5-yl)piperidine (Compd. No. 2185)

[0341] 4-[[N-(2-Amino-5-trifluoromethylbenzoyl)glycyl]aminomethyl]-1-(benzo[c]thiadiazol-5-yl)piperidine (Compd. No. 2185) was synthesized by using the corresponding starting material and reactants according to the method of Example 1875. 7.2 mg, 28% yield; ESI/MS m/e 507.4 (M⁺+H, C₂₃H₂₅F₃N₆O₂S).

[Example 1877] Synthesis of 4-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]aminomethyl]-1-(2-amino-4-chlorobenzyl)piperidine (Compd. No. 1919)

[0342] A mixture of 4-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]aminomethyl]piperidine (0.050 mmol) with 4-chloro-2-nitrobenzyl chloride (0.050 mmol), a piperidinomethylpolystyrene (60 mg), acetonitrile (1.0 mL) and chloroform (0.7 mL) was stirred at 50 °C overnight, cooled, then loaded onto a Varian™ SCX column and washed with chloroform/methanol (10 mL) and methanol (10 mL). The obtained product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. Ethanol (3 mL) and a 10% palladium carbon (15 mg) were added to the resulting residue, and the obtained mixture was stirred at room temperature under a hydrogen atmosphere for 1.5 hours and filtered. The filtrate was concentrated and then purified by preparative TLC to thereby afford 4-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]aminomethyl]-1-(2-amino-4-chlorobenzyl)piperidine (Compd. No. 1919) (5.1 mg, 14%). The purity was determined by RPLC/MS (90%). ¹H NMR (400MHz, CDCl₃) δ 1.09-1.32 (m, 4H), 1.41-1.59 (m, 1H), 1.66 (d, J = 12.5 Hz, 2H), 1.88 (t, J = 11.5 Hz, 2H), 2.82 (d, J = 11.5 Hz, H), 3.17 (t, J = 6.5 Hz, 2H), 3.42 (s, 2H), 4.05 (d, J = 3.5 Hz, 2H), 4.85 (br s, 1H), 5.92 (br s, 2H), 6.25-6.36 (m, 1H), 6.55-6.66 (m, 1H), 6.70 (d, J = 8.5 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 7.26 (s, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.68 (s, 1H); ESI/MS m/e 498.2 (M⁺+H, C₂₃H₂₇ClF₃N₅O₂).

[Examples 1878 to 1879]

[0343] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1877. Data of ESI/MS and yields (mg) and yields (%) in the final steps are collectively shown in Table 46.

Table 46

Example	Compd. No	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1878	1920	C ₂₂ H ₂₆ ClF ₂ N ₅ O ₂	466.2	3.5	10.0
1879	1922	C ₂₃ H ₂₇ ClF ₃ N ₅ O ₃	514.2	1.2	3.1

[Example 1880] Synthesis of 4-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]aminomethyl]-1-(benz[d]oxazol-5-yl)piperidine (Compd. No. 2188)

[0344] Triethyl orthoformate (0.033 mL, 3.3 equivalents) and pyridinium p-toluenesulfonate (2 mg, 0.4 equivalent) were added to a THF (2 mL) solution of 1-(3-amino-4-hydroxybenzyl)-4-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]aminomethyl]piperidine (34.8 mg, 0.060 mL) synthesized according to the method of Example 1826. The resulting mixture was stirred under reflux overnight and cooled to room temperature. The obtained mixture was then concentrated, and the resulting residue was dissolved in ethyl acetate, loaded onto a Bond Elut™ Si column,

eluted with ethyl acetate/methanol = 4:1 and concentrated.

[0345] The obtained residue was dissolved in ethyl acetate (1.5 mL), and a 4 M dioxane solution of HCl (0.5 mL) was added to the obtained solution. The resulting mixture was stirred at room temperature overnight, then adjusted to pH10 with a 5 M aqueous solution of NaOH and extracted with ethyl acetate. The extracts was concentrated and purified by preparative TLC (SiO₂, ethyl acetate/methanol = 4:1) to thereby provide 4-[[N-(2-amino-5-trifluoromethyl-benzoyl)glycyl]aminomethyl]-1-(benz[d]oxazol-5-yl)piperidine (Compd. No. 2188) (1.6 mg, 5%). The purity was determined by RPLC/MS (94%). ESI/MS m/e 490.3 (M⁺+H, C₂₄H₂₆F₃N₅O₃).

[Example 1881] Synthesis of 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)piperidine (Compd. No. 2190)

[0346] Phenyl chloroformate (0.040 mL) was added to a mixture of 1-(3-amino-4-hydroxy)-4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (22 mg, 0.040 mmol) with NaHCO₃ (0.040 mmol), water (0.7 mL) and methanol (1.5 mL), and the resulting mixture was stirred at room temperature for 3 hours. A 1 M aqueous solution of NaOH (0.040 mL) was added, and the obtained mixture was further stirred for 1.5 hours. The mixture was then extracted with ethyl acetate, and the extracts was concentrated. The resulting residue was dissolved in methanol, loaded onto a Varian™ SCX column and washed with methanol (5 mL×2). The obtained product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. A dichloromethane (2 mL) solution of chlorotrimethylsilane (1 M) and phenol (1 M) was added to the obtained residue. The mixture was stirred at room temperature for 2 hours and concentrated. The resulting residue was dissolved in methanol, loaded onto a Varian™ SCX column and washed with methanol (5 mL×2). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL), concentrated and purified by preparative TLC (SiO₂, ethyl acetate/methanol = 5:2) to thereby afford 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)piperidine (Compd. No. 2190) (4.1 mg, 22%). The purity was determined by RPLC/MS (100%). ESI/MS m/e 474.2 (M⁺+H, C₂₃H₂₅F₂N₅O₄).

[Examples 1882 to 1884]

[0347] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1881 (phenyl chlorothioformate was used in place of the phenyl chloroformate for synthesizing Compd. Nos. 2192 and 2193). Data of ESI/MS and yields (mg) and yields (%) in the final steps are collectively shown in Table 47.

Table 47

Example	Compd. No.	Chemical Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1882	2191	C ₂₄ H ₂₆ F ₃ N ₅ O ₄	506.3	3.1	10
1883	2192	C ₂₃ H ₂₅ F ₂ N ₅ O ₃ S	490.2	6.9	35
1884	2193	C ₂₄ H ₂₆ F ₃ N ₅ O ₃ S	522.2	3.6	11

[Reference Example 36] 4-[[N-(1-(9-fluorenylmethoxycarbonyl)piperidin-4-ylmethyl)carbamoylmethyl]aminomethyl]-3-methoxyphenyloxymethyl-polystyrene

[0348] Acetic acid (0.3 mL), sodium triacetoxymethylborohydride (1.92 g) and 4-formyl-3-(methoxyphenyloxymethyl)-polystyrene (1 mmol/g, 200 g) were added to a DMF (65 mL) solution of 1-(9-fluorenylmethoxycarbonyl)-4-(glycylaminomethyl)piperidine hydrochloride (10 mmol), and the resulting mixture was shaken for 2 hours and then filtered. The resin was washed with methanol, DMF, dichloromethane and methanol and dried to provide the objective substance.

[Examples 1885 to 2000] Solid-phase synthesis of 4-aminomethylpiperidines

[0349] Diisopropylethylamine (3.6 mmol) was added to a mixture of the corresponding carboxylic acid (1.6 mmol) with HBTU (1.6 mmol) and DMF (6 mL), and the resulting mixture was shaken for 2 minutes. 4-[[N-(1-(9-Fluorenylmethoxycarbonyl)piperidin-4-ylmethyl)carbamoylmethyl]aminomethyl]-3-methoxyphenyloxymethylpolystyrene (0.4 mmol) was added to the resulting mixture, and the obtained mixture was shaken for 1 hour and filtered. The resin was washed with dichloromethane and dried.

[0350] A mixture of NaBH(OAc)₃ (0.25 mmol) with acetic acid (0.025 mmol) and DMF was added to the obtained resin (0.05 mmol), and the corresponding aldehyde (2.5 mmol) was further added. The resulting mixture was shaken for 2 hours, then filtered and washed with methanol, a 10% DMF solution of diisopropylethylamine, DMF, dichlorometh-

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ane and methanol. A mixture of the resin with water (0.050 mL) and trifluoroacetic acid (0.95 mL) was shaken for 1 hour and filtered. The resin was washed with dichloromethane and methanol. The filtrate and washings were combined and concentrated. The resulting residue was loaded onto a Varian™ SCX column and washed with methanol (15 mL). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. The obtained product, if necessary, was purified by preparative TLC or HPLC to provide the objective compounds. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 48.

Table 48

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1885	1923	C ₂₃ H ₂₅ BrF ₃ N ₃ O ₂ S	544	15.7	87
1886	1924	C ₂₄ H ₂₈ F ₃ N ₃ O ₃ S	496	14.6	89
1887	1925	C ₂₃ H ₂₅ F ₄ N ₃ O ₂ S	484	11.7	73
1888	1926	C ₂₃ H ₂₄ F ₅ N ₃ O ₂ S	502	13.9	84
1889	1927	C ₂₃ H ₂₆ F ₃ N ₃ O ₃ S	482	10.7	67
1890	1928	C ₂₄ H ₂₆ F ₃ N ₃ O ₄ S	510	14.3	85
1891	1929	C ₂₆ H ₃₀ F ₃ N ₃ O ₂ S	506	14.7	88
1892	1930	C ₂₄ H ₂₈ F ₃ N ₃ O ₂ S ₂	512	14.4	85
1893	1931	C ₂₅ H ₃₀ F ₃ N ₃ O ₂ S	494	14.3	88
1894	1932	C ₂₅ H ₂₈ F ₃ N ₃ O ₃ S	509	7.1*	35
1895	1933	C ₂₅ H ₃₀ F ₃ N ₃ O ₂ S	494	14.3	88
1896	1934	C ₂₆ H ₃₂ F ₃ N ₃ O ₂ S	509	14.4	86
1897	1935	C ₂₃ H ₂₅ F ₃ N ₄ O ₄ S	511	14.9	88
1898	1936	C ₂₄ H ₂₈ F ₃ N ₃ O ₂ S	480	13.3	84
1899	1937	C ₂₆ H ₃₂ F ₃ N ₃ O ₂ S	509	11.1	66
1900	1938	C ₂₃ H ₂₇ Br ₂ N ₃ O ₂	538	5.3*	25
1901	1939	C ₂₄ H ₃₀ BrN ₃ O ₃	488	5.0*	25
1902	1940	C ₂₃ H ₂₇ BrFN ₃ O ₂	476	4.9*	25
1903	1941	C ₂₃ H ₂₆ BrF ₂ N ₃ O ₂	494	6.1*	30
1904	1942	C ₂₃ H ₂₈ BrN ₃ O ₃	474	1.7*	9
1905	1943	C ₂₄ H ₂₈ BrN ₃ O ₄	502	6.6*	32
1906	1944	C ₆ H ₃₂ BrN ₃ O ₂	498	7.0*	35
1907	1945	C ₂₄ H ₃₀ BrN ₃ O ₂ S	504	11.1	67
1908	1946	C ₂₅ H ₃₂ BrN ₃ O ₂	488	3.2*	16
1909	1947	C ₂₅ H ₃₀ BrN ₃ O ₃	500	5.7	35
1910	1948	C ₂₅ H ₃₂ BrN ₃ O ₂	486	4.9*	25
1911	1949	C ₂₆ H ₃₄ BrN ₃ O ₂	500	6.7*	33
1912	1950	C ₂₃ H ₂₇ BrN ₄ O ₄	503	5.0*	25
1913	1951	C ₂₄ H ₃₀ BrN ₃ O ₂	472	5.1*	26
1914	1952	C ₂₂ H ₂₄ Br ₂ FN ₃ O ₂	542	14.9	83
1915	1953	C ₂₃ H ₂₇ BrFN ₃ O ₃	492	13.9	86
1916	1954	C ₂₂ H ₂₄ BrF ₂ N ₃ O ₂	480	12.5	79

Note: * indicates "yield (mg) of trifluoroacetate".

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Table 48 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	1917	C ₂₂ H ₂₃ BrF ₃ N ₃ O ₂	498	13.2	80
	1918	C ₂₂ H ₂₅ BrFN ₃ O ₃	478	7.0	44
	1919	C ₂₃ H ₂₅ BrFN ₃ O ₄	506	4.0*	20
10	1920	C ₂₅ H ₂₉ BrFN ₃ O ₂	502	14.6	88
	1921	C ₂₃ H ₂₇ BrFN ₃ O ₂ S	508	13.1	78
	1922	C ₂₄ H ₂₉ BrFN ₃ O ₂	490	13.8	85
15	1923	C ₂₄ H ₂₇ BrFN ₃ O ₃	504	2.7*	13.
	1924	C ₂₄ H ₂₉ BrFN ₃ O ₂	490	12.7	78
	1925	C ₂₅ H ₃₁ BrFN ₃ O ₂	504	13.5	81
20	1926	C ₂₂ H ₂₄ BrFN ₄ O ₄	507	14.8	88
	1927	C ₂₃ H ₂₇ BrFN ₃ O ₂	476	12.1	77
	1928	C ₂₅ H ₃₁ BrFN ₃ O ₂	504	13.4	80
25	1929	C ₂₂ H ₂₆ BrFN ₄ O ₂	477	4.7*	20
	1930	C ₂₃ H ₂₉ FN ₄ O ₃	429	6.9*	32
	1931	C ₂₂ H ₂₇ FN ₄ O ₃	415	3.7*	17
30	1932	C ₂₃ H ₂₇ FN ₄ O ₄	443	5.4*	24
	1933	C ₂₅ H ₃₁ FN ₄ O ₂	439	4.3*	20
	1934	C ₂₃ H ₂₉ FN ₄ O ₂ S	445	6.2*	28
35	1935	C ₂₄ H ₃₁ FN ₄ O ₂	427	6.3*	29
	1936	C ₂₄ H ₃₁ FN ₄ O ₂	427	4.9*	23
	1937	C ₂₂ H ₂₆ FN ₅ O ₄	444	5.9*	27
40	1938	C ₂₃ H ₂₉ FN ₄ O ₂	413	6.7*	32
	1939	C ₂₃ H ₂₆ FN ₅ O ₂	424	5.1*	24
	1940	C ₂₅ H ₃₃ FN ₄ O ₂	441	6.3*	29
45	1941	C ₂₅ H ₃₀ F ₂ N ₄ O ₂	457	8.0*	35
	1942	C ₂₄ H ₂₈ F ₂ N ₄ O ₃	459	6.0*	26
	1943	C ₂₂ H ₂₅ F ₂ N ₅ O ₄	462	9.3*	41
50	1944	C ₂₃ H ₂₅ F ₂ N ₅ O ₂	442	6.0*	27
	1945	C ₂₅ H ₃₂ F ₂ N ₄ O ₂	459	8.3*	37
	1946	C ₂₂ H ₂₆ BrIN ₄ O ₂	585	9.7*	36
55	1947	C ₂₃ H ₂₉ IN ₄ O ₃	537	9.2*	36
	1948	C ₂₂ H ₂₇ IN ₄ O ₃	523	5.8*	23
	1949	C ₂₃ H ₂₇ IN ₄ O ₄	551	8.2*	32
	1950	C ₂₅ H ₃₁ IN ₄ O ₂	547	6.7*	26
	1951	C ₂₃ H ₂₉ IN ₄ O ₂ S	553	6.4*	25
	1952	C ₂₄ H ₃₁ IN ₄ O ₂	535	7.2*	29
	1953	C ₂₄ H ₂₉ IN ₄ O ₃	549	5.6*	22

Note: * indicates "yield (mg) of trifluoroacetate".

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Table 48 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
5	1954	C ₂₄ H ₃₁ IN ₄ O ₂	535	6.2*	25
	1955	C ₂₂ H ₂₆ IN ₅ O ₄	552	10.2*	40
	1956	C ₂₃ H ₂₉ IN ₄ O ₂	521	7.5*	30
10	1957	C ₂₃ H ₂₆ IN ₅ O ₂	532	6.8*	27
	1958	C ₂₅ H ₃₃ IN ₄ O ₂	549	7.1*	28
	1959	C ₂₅ H ₃₃ IN ₄ O ₂	549	3.0*	12
15	1960	C ₂₂ H ₂₅ BrClN ₃ O ₂	478	7.6*	39
	1961	C ₂₃ H ₂₈ ClN ₃ O ₃	430	7.0*	39
	1962	C ₂₂ H ₂₅ ClFN ₃ O ₂	418	14.1	102
20	1963	C ₂₂ H ₂₆ ClN ₃ O ₃	416	6.3*	36
	1964	C ₂₃ H ₂₆ ClN ₃ O ₄	444	7.1*	39
	1965	C ₂₅ H ₃₀ ClN ₃ O ₂	440	15.3	105
25	1966	C ₂₃ H ₂₈ ClN ₃ O ₂ S	446	8.4*	45
	1967	C ₂₄ H ₃₀ ClN ₃ O ₂	428	7.4*	41
	1968	C ₂₄ H ₃₀ ClN ₃ O ₂	428	13.8	98
30	1969	C ₂₂ H ₂₅ ClN ₄ O ₄	445	16.0	109
	1970	C ₂₃ H ₂₈ ClN ₃ O ₂	414	14.1	103
	1971	C ₂₃ H ₂₅ ClN ₄ O ₂	425	14.8	106
35	1972	C ₂₅ H ₃₂ ClN ₃ O ₂	442	14.5	99
	1973	C ₂₅ H ₃₂ ClN ₃ O ₂	442	14.5	99
	1974	C ₂₂ H ₂₄ Br ₂ ClN ₃ O ₂	558	12.8*	58
40	1975	C ₂₃ H ₂₇ BrClN ₃ O ₃	508	8.6*	42
	1976	C ₂₂ H ₂₅ BrClN ₃ O ₃	494	6.0*	30
	1977	C ₂₃ H ₂₅ BrClN ₃ O ₄	522	8.4*	40
45	1978	C ₂₅ H ₂₉ BrClN ₃ O ₂	518	17.6	103
	1979	C ₂₃ H ₂₇ BrClN ₃ O ₂ S	524	17.1	99
	1980	C ₂₄ H ₂₉ BrClN ₃ O ₂	506	14.7	88
50	1981	C ₂₄ H ₂₇ BrClN ₃ O ₃	520	8.0*	38
	1982	C ₂₄ H ₂₉ BrClN ₃ O ₂	506	14.7	88
	1983	C ₂₂ H ₂₄ BrClN ₄ O ₄	523	12.0*	57
55	1984	C ₂₃ H ₂₇ BrClN ₃ O ₂	492	8.5*	42
	1985	C ₂₃ H ₂₄ BrClN ₄ O ₂	503	6.3*	31
	1986	C ₂₅ H ₃₁ BrClN ₃ O ₂	520	9.6*	46
	1987	C ₂₅ H ₃₁ BrClN ₃ O ₂	520	15.0	87
	1988	C ₂₂ H ₂₃ BrClF ₂ N ₃ O ₂	514	15.8	93
	1989	C ₂₂ H ₂₆ Br ₂ N ₄ O ₂	537	10.7*	42
	1990	C ₂₃ H ₂₉ BrN ₄ O ₃	489	8.5*	36

Note: * indicates "yield (mg) of trifluoroacetate".

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Table 48 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1991	2029	C ₂₂ H ₂₇ BrN ₄ O ₃	475	7.5*	32
1992	2030	C ₂₃ H ₂₇ BrN ₄ O ₄	503	6.8*	28
1993	2031	C ₂₅ H ₃₁ BrN ₄ O ₂	499	6.2*	26
1994	2032	C ₂₄ H ₂₉ BrN ₄ O ₃	501	8.9*	37
1995	2033	C ₂₄ H ₃₁ BrN ₄ O ₂	487	9.1*	39
1996	2034	C ₂₂ H ₂₆ BrN ₅ O ₄	504	6.4*	26
1997	2035	C ₂₃ H ₂₉ BrN ₄ O ₂	473	6.5*	28
1998	2036	C ₂₃ H ₂₆ BrN ₅ O ₂	484	6.3*	27
1999	2037	C ₂₅ H ₃₃ BrN ₄ O ₂	501	5.4*	22
2000	2038	C ₂₂ H ₂₅ BrF ₂ N ₄ O ₂	495	5.4*	23

Note: * indicates "yield (mg) of trifluoroacetate".

[Example 2001] Synthesis of 1-(3-carbamoylbenzyl)-4-[[N-(3-trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine (Compd. No. 924)

[0351] EDCI (10.7 mg), 1-hydroxybenzotriazole hydrate (7.5 mg), triethylamine (15.4 mg), a 0.5 M dioxane solution of NH₃ (0.1 mL, 0.05 mmol) and DMF (0.5 mL) were added to a chloroform (2.5 mL) solution of 1-(3-carboxybenzyl)-4-[[N-(3-trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine (19.4 mg, 0.041 mmol), and the resulting mixture was shaken at 25 °C for 20 hours and then washed with a 2 M aqueous solution of NaOH (2×2 mL) and brine (1 mL). The organic layer was filtered through a PTFE membrane filter, and the solvent was then removed under reduced pressure to provide 1-(3-carbamoylbenzyl)-4-[[N-(3-trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine (Compd. No. 924) as an off-white solid (17.9 mg, 92%). The purity was determined by RPLC/MS (89%). ESI/MS m/e 447.3 (M⁺+H, C₂₄H₂₇F₃N₄O₃).

[Example 2002] Synthesis of 1-(4-carbamoylbenzyl)-4-[[N-(3-trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine (Compd. No. 925)

[0352] The Compd. No. 925 was synthesized by using the corresponding starting material and reactants according to the method of Example 2001. 14.2 mg, 72%. The purity was determined by RPLC/MS (86%). ESI/MS m/e 447 (M⁺+H, C₂₄H₂₇F₃N₄O₃).

[Example 2003] Synthesis of 1-(4-aminobenzyl)-4-[[N-(3-trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine (Compd. No. 516)

[0353] An ethanol (3 mL) solution of 1-(4-nitrobenzyl)-4-[[N-(3-trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine (22.4 mg, 0.047 mmol) was hydrogenated in the presence of a 5% palladium carbon (10 mg) at 25 °C in a hydrogen atmosphere under 1 atm for 1 hour. The catalyst was removed by filtration, and washed with ethanol (5 mL). The filtrates were collected and concentrated to thereby afford 1-(4-aminobenzyl)-4-[[N-(3-trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine (Compd. No. 516) as an off-white solid (20.1 mg, 96%). The purity was determined by RPLC/MS (99%). ESI/MS m/e 449.1 (M⁺+H, C₂₃H₂₇F₃N₄O₂).

[Examples 2004 to 2005]

[0354] Compd. Nos. 517 and 518 were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 2003. Data of ESI/MS and yields (mg) and yields (%) in the final steps are collectively shown in Table 49.

Table 49

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
2004	517	C ₂₃ H ₂₇ F ₃ N ₄ O ₂	449	26.5	78
2005	518	C ₂₃ H ₂₇ F ₃ N ₄ O ₂	449	25.3	71

[Example 2006] Synthesis of 1-[4-(benzoylamino)benzyl]-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (Compd. No. 519)

[0355] EDCI (4.7 mg), 1-hydroxybenzotriazole hydrate (3.3 mg), triethylamine (2.5 mg) and benzoic acid (3.0 mg) were added to a dichloromethane (2.5 mL) solution of 1-(4-aminobenzyl)-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (10.1 mg, 0.023 mmol), and the resulting mixture was shaken at 25 °C for 16 hours. The reaction mixture was washed with a 2 M aqueous solution of NaOH (2 mL×2) and brine (1 mL) and then filtered through a PTFE membrane filter. The solvent was evaporated under reduced pressure to thereby provide yellow oil. The obtained yellow oil was purified by preparative TLC (SiO₂, 10% methanol/dichloromethane) to afford 1-[4-(benzoylamino)benzyl]-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (Compd. No. 519) as a colorless oil (4.6 mg, 36%). The purity was determined by RPLC/MS (99%). ESI/MS m/e 553.2 (M⁺+H, C₃₀H₃₁F₃N₄O₃).

[Example 2007] Synthesis of 1-[4-(piperidinocarbonyl)benzyl]-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (Compd. No. 1572)

[0356] Piperidine (0.048 mg), and a DMF (0.15 mL) solution of diisopropylcarbodiimide (0.45 mmol) and 1-hydroxybenzotriazole hydrate (0.45 mmol) were added to a DMF (1.0 mL) solution of 1-(4-carboxybenzyl)-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (0.040 mmol), and the resulting mixture was shaken at room temperature for 17 hours, then loaded onto a Varian™ SCX column and washed with chloroform/methanol = 1:1 (5 mL) and methanol (5 mL). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated to thereby provide 1-[4-(piperidinocarbonyl)benzyl]-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (Compd. No. 1572) (14.3 mg, 66%). The purity was determined by RPLC/MS (99%). ESI/MS m/e 545 (M⁺+H, C₂₉H₃₅F₃N₄O₃).

[Examples 2008 to 2015]

[0357] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 2007. Data of ESI/MS and yields (mg) and yields (%) in the final steps are collectively shown in Table 50.

Table 50

Example	Compd. No	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
2008	1573	C ₃₁ H ₃₃ F ₃ N ₄ O ₄	583	17.6	76
2009	1574	C ₃₁ H ₃₃ F ₃ N ₄ O ₃	567	18.8	83
2010	1575	C ₃₀ H ₃₀ ClF ₃ N ₄ O ₃	587	3.2	14
2011	1576	C ₂₈ H ₃₃ F ₃ N ₄ O ₄	547	21.1	97
2012	1577	C ₂₆ H ₃₁ F ₃ N ₄ O ₄	521	5.1	24
2013	1578	C ₃₁ H ₃₃ F ₃ N ₄ O ₃	567	16.9	75
2014	1579	C ₃₁ H ₃₃ F ₃ N ₄ O ₃	567	6.0	26
2015	1580	C ₂₉ H ₃₅ F ₃ N ₄ O ₃	545	15.1	69

[Example 2016] Synthesis of 1-[4-(chloroformyl)benzyl]-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine

[0358] A mixture of 1-(4-carboxybenzyl)-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (240 mg) with thionyl chloride (1 mL) was stirred at room temperature for 12 hours, and the excess thionyl chloride was removed under reduced pressure to thereby afford 1-[4-(chloroformyl)benzyl]-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminome-

thyl]piperidine. The resulting acid chloride was used without being further purified.

[Example 2017] Synthesis of 1-[4-[N-(2-methoxyethyl)carbamoyl]benzyl]-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (Compd. No. 1612)

[0359] A mixture of 1-[4-(chloroformyl)benzyl]-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (0.042 mmol) with 2-methoxyethylamine (3.8 mg, 0.050 mmol), a piperidinomethylpolystyrene (46 mg) and dichloromethane (1.5 mL) was stirred at room temperature for 17 hours. Water (0.020 mL) was then added to the mixture, and the resulting mixture was stirred for 30 minutes. Methanol (1 mL) was then added to the obtained mixture, and the resulting mixture was loaded onto a Varian™ SCX column and washed with methanol (10 mL). The obtained crude product was eluted with a 2 M methanol solution of NH₃ and concentrated to thereby provide 1-[4-[N-(2-methoxyethyl)carbamoyl]benzyl]-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (Compd. No. 1612) (26.7 mg, 100%). The purity was determined by RPLC/MS (92%). ESI/MS m/e 535.2 (M⁺+H, C₂₇H₃₃F₃N₄O₄).

[Examples 2018 to 2020]

[0360] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to Example 2017. The obtained products, if necessary, were purified by preparative TLC to afford the objective compounds. Data of ESI/MS and yields (mg) and yields (%) are collectively shown in Table 51.

Table 51

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
2018	1610	C ₃₁ H ₃₀ F ₆ N ₄ O ₃	621.2	4.4	14
2019	1611	C ₃₀ H ₂₉ Cl ₂ F ₃ N ₄ O ₃	621.2	35.7	Q
2020	1613	C ₃₂ H ₃₅ F ₃ N ₄ O ₃	581.2	29.9	Q
Note: Q means "Quantitative".					

[Example 2021] Synthesis of 4-[N-[5-bromo-2-(methylamino)benzoyl]glycyl]aminomethyl-1-(4-chlorobenzyl)piperidine (Compd. No. 1427)

[0361] A triethyl orthoformate (6.5 mL) solution of 4-[N-(2-amino-5-bromobenzoyl)glycyl]aminomethyl-1-(4-chlorobenzyl)piperidine (Compd. No. 1042) (50 mg, 0.10 mmol) was stirred at 150 °C for 17 hours and concentrated to thereby provide a yellow solid. Sodium borohydride (7.6 mg, 0.2 mmol) was added to an ethanol (3 mL) solution of the yellow solid, and the mixture was stirred at room temperature for 14 hours. The resulting white precipitate was dissolved in dichloromethane, and the obtained solution was washed with a 1 M aqueous solution of NaOH (2 mL). The organic layer was separated, dried over K₂CO₃, filtered and concentrated, and the obtained crude product was purified by column chromatography (SiO₂, 20% methanol/chloroform) to provide 4-[N-[5-bromo-2-(methylamino)benzoyl]glycyl]aminomethyl-1-(4-chlorobenzyl)piperidine (Compd. No. 1427) (40 mg, 80%). The purity was determined by RPLC/MS (100%). ESI/MS m/e 505 (M⁺+H, C₂₃H₂₈BrClF₆N₄O₂).

[Example 2022] Synthesis of 4-[N-[5-bromo-2-(dimethylamino)benzoyl]glycyl]aminomethyl-1-(4-chlorobenzyl)piperidine (Compd. No. 1428)

[0362] Sodium cyanoborohydride (26 mg, 0.42 mmol) and acetic acid (14 mL) were added to a mixture of 4-[N-(2-amino-5-bromobenzoyl)glycyl]aminomethyl-1-(4-chlorobenzyl)piperidine (Compd. No. 1042) (67 mg, 0.14 mmol) with a 37% aqueous solution of formaldehyde (0.112 mL, 1.4 mmol), acetonitrile (2 mL) and methanol (1.5 mL), and the resulting mixture was stirred at 50 °C for 30 hours. A 1 M aqueous solution of NaOH and dichloromethane were added to the mixture. The aqueous layer was separated, and the organic layer was dried over K₂CO₃, filtered, concentrated and purified by column chromatography (SiO₂, 20% methanol/ethyl acetate) to afford 4-[N-[5-bromo-2-(dimethylamino)benzoyl]glycyl]aminomethyl-1-(4-chlorobenzyl)piperidine (Compd. No. 1428) (60 mg, 82%). The purity was determined by RPLC/MS (100%). ESI/MS m/e 523 (M⁺+H, C₂₄H₃₀BrClF₆N₄O₂).

[Example 2023] Synthesis of 4-[[N-[5-bromo-2-(methylsulfonylamino)benzoyl]glycyl]aminomethyl]-1-(4-chlorobenzyl)piperidine (Compd. No. 1581)

[0363] A mixture of 4-[[N-[2-amino-5-bromobenzoyl]glycyl]aminomethyl]-1-(4-chlorobenzyl)piperidine (25 mg, 0.05 mmol) with methanesulfonyl chloride (0.0045 mL), triethylamine (0.026 mL) and dichloromethane (2 mL) was stirred at room temperature for 17 hours. The resulting reaction mixture was purified by column chromatography (SiO₂), loaded onto a Varian™ SAX column and washed with methanol (5 mL). The obtained crude product was eluted with a 0.1 M methanol solution of HCl (5 mL) and concentrated to thereby provide 4-[[N-[5-bromo-2-(methylsulfonylamino)benzoyl]glycyl]aminomethyl]-1-(4-chlorobenzyl)piperidine (Compd. No. 1581) (5.4 mg, 19%). ESI/MS m/e 573.0 (M⁺+H, C₂₃H₂₈BrClN₄O₄S).

[Example 2024] Synthesis of 4-[[N-[5-bromo-2-(bis(methylsulfonyl)amino)benzoyl]glycyl]aminomethyl]-1-(4-chlorobenzyl)piperidine (Compd. No. 1582)

[0364] A mixture of 1-(4-chlorobenzyl)-4-[[N-[2-amino-5-bromobenzoyl]glycyl]aminomethyl]piperidine (57 mg, 0.10 mmol) with methanesulfonyl chloride (0.018 mL, 0.024 mmol), triethylamine (0.068 mL) and dichloromethane (2 mL) was stirred at room temperature for 8 hours. A 1 M aqueous solution of NaOH (1 mL) was added to the mixture, and the resulting mixture was extracted with dichloromethane (2 mL×3). The extracts were combined, dried over K₂CO₃, filtered, concentrated and purified by column chromatography (SiO₂) to afford 4-[[N-[5-bromo-2-(bis(methylsulfonyl)amino)benzoyl]glycyl]aminomethyl]-1-(4-chlorobenzyl)piperidine (Compd. No. 1582) (40 mg, 62%). ESI/MS m/e 651 (M⁺+H, C₂₄H₃₀BrClN₄O₆S₂).

[Example.2025] Synthesis of 1-(4-chlorobenzyl)-1-methyl-4-[[N-(3-(trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidinium iodide (methylammonium iodide of Compd. No. 461)

[0365] An acetonitrile (1.0 mL) solution of 4-[[N-[3-(trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine (30 mg, 0.087 mmol) and a (piperidinomethyl)polystyrene (80 mg, 2.7 mmol base/g resin) were added to a chloroform (1.0 mL) solution of 4-chlorobenzyl chloride (11.7 mg, 0.073 mmol), and the resulting mixture was stirred at 60 °C for 2 hours. Phenyl isocyanate (10.4 mg, 0.087 mmol) was then added to the reaction mixture cooled to room temperature, and the obtained mixture was stirred at 25 °C for 1 hour, then loaded onto a Varian™ SCX column and washed with methanol (20 mL). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (6 mL) and concentrated to thereby provide 1-(4-chlorobenzyl)-4-[[N-[3-(trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine as a colorless oil.

[0366] Methyl iodide (28 mg, 0.20 mmol) was added to an acetonitrile (2.0 mL) solution of 1-(4-chlorobenzyl)-4-[[N-[3-(trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine. The resulting reaction mixture was stirred at 70 °C for 4 hours. The solvent was removed under reduced pressure to provide 1-(4-chlorobenzyl)-1-methyl-4-[[N-[3-(trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidinium iodide as yellow oil. (31.7 mg, 71%). The purity was determined by RPLC/MS (99%). ESI/MS m/e 482.1 (M⁺+H, C₂₄H₂₈ClF₃N₃O₂).

[Example 2026] Synthesis of 1-(4-chlorobenzyl)-4-[N-methyl-N-[N-(3-(trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine (Compd. No. 520)

[0367] An aqueous solution of formaldehyde (108 mg, 1.33 mmol, 37 wt.%) was added to a 10% acetic acid/methanol (3 mL) solution of 1-(4-chlorobenzyl)-4-(aminomethyl)piperidine (318 mg, 1.33 mmol) and NaBH₃CN (668 mg), and the resulting mixture was stirred at 25 °C for 1 hour. The reaction mixture was loaded onto a Dowex™ 50Wx2 column (10 mL) and washed with methanol (20 mL). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (6 mL) and concentrated to thereby afford 1-(4-chlorobenzyl)-4-[(methylamino)methyl]piperidine as a colorless oil. The resulting oil was used without being purified.

[0368] EDCI (85 mg) and 1-hydroxybenzotriazole hydrate (60 mg) were added to a dichloromethane (4 mL) solution of 1-(4-chlorobenzyl)-4-[(methylamino)methyl]piperidine (111 mg, 0.44 mmol), and the resulting mixture was stirred at 25 °C for 1 hour, then washed with a 2 M aqueous solution of NaOH (2 mL×2) and filtered through a PTFE membrane filter. The solvent was subsequently removed under reduced pressure to provide a yellow oil, which was then purified by preparative TLC to afford 1-(4-chlorobenzyl)-4-[N-methyl-N-[N-(3-(trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine (Compd. No. 520) as an off-white oil (14.0 mg, 3.4%). The purity was determined by RPLC/MS (99%). ESI/MS m/e 482.1 (M⁺+H, C₂₄H₂₇ClF₃N₃O₂).

[Reference Example 37] Synthesis of 3-aminohomopiperidine

[0369] A 1 M BH₃-THF solution (80 mL) was added to a THF (70 mL) solution of DL-α-amino-ε-caprolactam (2 g, 16

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mmol), and the resulting mixture was refluxed for 3 hours. A 2 M hydrochloric acid (50 mL) was added, and the reaction mixture was further heated and refluxed for 1 hour and then cooled to 25°C. A 4 M NaOH solution was added to basicify the reaction mixture (pH10), and the resulting mixture was extracted with ethyl acetate (200 mL×3). The organic layers were combined, washed with a saturated aqueous NaHCO₃, dried (over MgSO₄) and concentrated to thereby provide the objective compound (990 mg, 54%). The obtained compounds was used without being purified.

[Reference Example 38] Synthesis of 3-amino-1-(4-chlorobenzyl)homopiperidine

[0370] p-Chlorobenzyl chloride (463 mg, 2.9 mmol) and K₂CO₃ (828 g, 6 mmol) were added to an acetonitrile (45 mL) solution of 3-aminohomopiperidine (1.71 g, 15 mmol), and the resulting mixture was stirred at 70 °C with heating for 9 hours, cooled to 25 °C and concentrated to afford a yellow solid. The resulting residue was partitioned between H₂O (5 mL) and ethyl acetate (50 mL) and the aqueous layer was extracted with ethyl acetate (50 mL×2). The organic layers were combined, washed with brine (20 mL), dried (over MgSO₄) and concentrated. The obtained yellow oil was purified by column chromatography (SiO₂, 5-20% methanol/dichloromethane gradient elution) to afford the objective compounds as yellow oil (639 mg, 93%).

[Example 2027] Synthesis of 1-(4-chlorobenzyl)-3-[(4-benzoylbutyryl)amino]homopiperidine (Compd. No. 994)

[0371] EDCI (23 mg), HOBt (16.2 mg) and triethylamine (15.2 μ L) were added to a chloroform (1 mL) solution of 3-amino-1-(4-chlorobenzyl)homopiperidine (24 mg, 0.10 mmol) and 4-benzoylbutyric acid (1.2 equivalents), and the resulting mixture was stirred at 25 °C for 16 hours. The reaction mixture was diluted with dichloromethane (0.5 mL), filtered through a PTFE membrane and concentrated to provide 1-(4-chlorobenzyl)-3-[(4-benzoylbutyryl)amino]homopiperidine (Compd. No. 994) (43 mg, 99%). The purity was determined by RPLC/MS (98%). ESI/MS m/e 413 (M⁺+H, C₂₄H₂₉ClN₂O₂).

[Examples 2028 to 2042]

[0372] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 2027. The obtained products, if necessary, were purified by chromatography (HPLC-C₁₈) to afford the objective compounds as TFA salts. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 52.

Table 52

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
2028	943	C ₂₃ H ₂₅ ClF ₃ N ₃ O ₂	468	6	28
2029	944	C ₂₃ H ₂₈ ClN ₃ O ₂	414	5	29
2030	945	C ₂₂ H ₂₅ ClN ₄ O ₄	445	6	30
2031	946	C ₂₃ H ₂₇ ClN ₄ O ₄	459	5	24
2032	947	C ₂₅ H ₃₁ ClN ₂ O ₄	459	4	20
2033	948	C ₂₄ H ₂₉ Cl ₂ N ₃ O ₂	462	6	32
2034	949	C ₂₅ H ₃₂ ClN ₃ O ₂	442	6	31
2035	988	C ₂₃ H ₂₅ ClF ₃ N ₃ O ₂	468	45	92
2036	989	C ₂₃ H ₂₈ ClN ₃ O ₃	430	44	97
2037	990	C ₂₂ H ₂₆ ClN ₃ O ₂	400	41	99
2038	991	C ₂₃ H ₂₇ ClN ₂ O ₂	399	41	97
2039	992	C ₂₅ H ₃₁ ClN ₂ O ₄	459	47	98
2040	993	C ₂₅ H ₃₁ ClN ₂ O ₂	427	44	98
2041	995	C ₂₅ H ₃₁ ClN ₂ O ₃	443	44	95
2042	996	C ₂₄ H ₃₁ ClN ₄ O ₂	443	5*	11

Note: * indicates "yield (mg) of trifluoroacetate".

[Example 2043] Measurement of inhibitory activity of test compounds against binding of MIP-1 α to THP-1 cells

[0373] THP-1 cells which are human monocytic leukemia cell line were suspended in an assay buffer [prepared by adding 0.1% of BSA and 25 mM of HEPES to RP1VII-1640 (Gibco-BRL Co.) and adjusting the pH to 7.4] so as to provide 1×10^7 cells/mL to thereby afford a cell suspension. A solution obtained by diluting the test compound with the assay buffer was used as a test compound solution. A solution prepared by diluting an iodine-labeled human MIP-1 α (DuPont NEN Co.) with the assay buffer so as to provide 250 nCi/mL was used as a labeled ligand solution. In a 96-well filter plate (Millipore Co.), were aliquoted 25 μ L of the test compound solution, 25 μ L of the labeled ligand solution and 50 μ L of the cell suspension in the order mentioned for each well. The solutions were stirred (100 μ L of the reaction solution) and then incubated at 18 °C for 1 hour.

[0374] After completing the reaction, the reaction solution was filtered through a filter, and the filter was washed with 200 μ L of cold PBS twice (the reaction solution was filtered after adding 200 μ L of the cold PBS). The filter was air-dried, and 25 μ L of liquid scintillator was then added into each well to count the radioactivity retained by the cells on the filter using TopCount (Packard Instrument Co.).

[0375] The count when 100 ng of an unlabeled human MIP-1 α (Peprotech Co.) instead of the test compound was added was subtracted as nonspecific adsorption, and the count when the test compound was not added was taken as 100%. Thereby, the inhibitory activity of the test compound against binding of the human MIP-1 α to THP-1 cells was calculated.

$$\text{Inhibition ratio (\%)} = [1 - (A - B) / (C - B)] \times 100$$

(wherein A is the count when the test compound is added; B is the count when 100 ng of the unlabeled human MIP-1 α is added; C is the count when only the [125 I]-labeled human MIP-1 α is added).

[0376] When the inhibitory activity of the cyclic amine derivatives which are active ingredients of the present invention was measured, for example, the following compounds respectively manifested an inhibitory activity of 20% to 50%, 50% to 80% and >80% at a concentration of 2 μ M or 10 μ M.

[0377] Compounds which manifested an inhibitory activity of 20% to 50% at a concentration of 10 μ M:

Compd. Nos. 29, 37, 41, 45, 46, 47, 50, 82, 85, 107, 120, 134, 214, 217, 218, 220, 222, 225, 226, 227, 228, 229, 230, 231, 233, 234, 236, 237, 238, 333, 334, 335, 336, 338, 340, 342, 347, 348, 349, 350, 352, 357, 359, 361, 366, 372, 374, 375, 376, 380, 382, 383, 385, 470, 471, 472, 473, 474, 483, 484, 488, 489, 491, 497, 499, 500, 502, 506, 508, 510, 514, 515, 518, 524, 543, 553, 554, 555, 556, 563, 571, 575, 576, 578, 579, 580, 583, 586, 587, 588, 590, 591, 592, 595, 596, 598, 603, 610, 611, 612, 614, 624, 625, 626, 629, 635, 638, 639, 640, 641, 642, 643, 644, 646, 647, 648, 649, 652, 653, 658, 659, 660, 665, 666, 669, 671, 675, 677, 679, 681, 682, 684, 691, 695, 696, 700, 702, 704, 706, 711, 712, 714, 717, 721, 723, 724, 726, 727, 728, 729, 731, 737, 739, 740, 741, 742, 744, 746, 765, 767, 772, 773, 774, 775, 776, 780, 781, 785, 786, 787, 788, 790, 791, 792, 793, 795, 796, 797, 798, 805, 806, 807, 810, 813, 820, 821, 822, 824, 825, 827, 829, 830, 833, 834, 837, 838, 844, 853, 855, 873, 877, 878, 880, 882, 887, 888, 891, 894, 901, 903, 904, 905, 911, 929, 932, 933, 935, 938, 940, 948, 993, 996, 1006, 1018, 1026, 1028, 1035, 1048, 1053, 1054, 1055, 1056, 1068, 1070, 1071, 1072, 1073, 1075, 1076, 1081, 1763 and 1764

[0378] Compounds which manifested an inhibitory activity of 50% to 80% at a concentration of 10 μ M:

Compd. Nos. 1, 2, 3, 4, 7, 13, 22, 23, 24, 25, 27, 31, 32, 38, 48, 83, 119, 121, 123, 131, 215, 216, 221, 235, 337, 351, 354, 358, 362, 363, 365, 367, 368, 369, 373, 378, 381, 384, 458, 459, 463, 465, 466, 467, 468, 478, 479, 480, 482, 485, 486, 487, 492, 493, 494, 495, 496, 498, 501, 503, 504, 507, 511, 512, 513, 520, 523, 527, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 545, 546, 547, 548, 549, 550, 551, 552, 558, 559, 560, 561, 562, 565, 567, 568, 569, 570, 572, 573, 574, 577, 581, 582, 594, 597, 599, 600, 602, 604, 606, 607, 608, 609, 613, 615, 616, 618, 619, 620, 621, 628, 630, 631, 632, 633, 634, 636, 637, 645, 651, 654, 655, 657, 661, 662, 664, 673, 674, 676, 678, 680, 683, 685, 687, 688, 689, 693, 703, 705, 707, 708, 709, 710, 713, 716, 718, 719, 720, 725, 730, 732, 733, 734, 735, 736, 749, 750, 751, 752, 753, 754, 756, 758, 760, 762, 763, 764, 766, 768, 769, 770, 771, 777, 778, 779, 784, 794, 799, 800, 802, 804, 808, 809, 811, 812, 815, 816, 819, 828, 831, 832, 835, 836, 839, 840, 845, 846, 847, 848, 850, 851, 854, 857, 858, 859, 860, 861, 862, 863, 865, 866, 867, 868, 872, 874, 876, 886, 899, 910, 942, 998, 1004, 1005, 1007, 1013, 1015, 1016, 1017, 1019, 1020, 1021, 1022, 1024, 1030, 1037, 1042, 1043, 1044, 1045, 1046, 1047, 1049, 1050, 1052, 1059, 1060, 1061, 1067, 1069, 1074, 1078, 1079, 1080 and 1766

[0379] Compounds which manifested an inhibitory activity of >80% at a concentration of 10 μ M:

Compd. Nos. 461, 464, 469, 481, 490, 505, 509, 521, 526, 528, 544, 564, 566, 601, 605, 617, 622, 623, 627, 650, 656, 663, 668, 672, 686, 690, 692, 694, 715, 743, 747, 748, 755, 757, 759, 761, 782, 783, 803, 814, 817, 818, 826, 849, 856, 864, 869, 870, 871, 999, 1000, 1001, 1002, 1003, 1008, 1009, 1010, 1011, 1012, 1023, 1029, 1031, 1032, 1033, 1034, 1036, 1038, 1039, 1040, 1041, 1051, 1057, 1058, 1062, 1063, 1064, 1065, 1066, 1082 and 1083

[0380] Compounds which manifested an inhibitory activity of 20% to 50% at a concentration of 2 μ M:

Compd. Nos. 1042, 1043, 1244, 1245, 1416, 1435, 1436, 1438, 1441, 1480, 1570, 1583, 1584, 1589, 1590, 1594, 1595, 1601, 1660, 1672, 1687, 1724, 1779, 1780, 1787, 1795, 1796, 1798, 1799, 1802, 1893, 1894, 1898, 1900, 1915, 1919, 1920, 2092, 2096, 2098 and 2100

[0381] Compounds which manifested an inhibitory activity of 50% to 80% at a concentration of 2 μ M:

Compd. Nos. 1190, 1414, 1600, 2091, 2094 and 2095

[0382] Compounds which manifested an inhibitory activity of >80% at a concentration of 2 μ M:

Compd. Nos. 2093, 2097, 2099, 2103 and 2104.

[Example 2044] Measurement of inhibitory activity against binding of MCP-1 to THP-1 cells

1. Preparation of human MCP-1 gene-carrying recombinant baculovirus

[0383] Two kinds of synthetic DNA primers (5'-CACTCTAGACTCCAGCATGA-3' and 5'-TAGCTGCAGATTCTT-GGGTTG-3') having restriction enzyme recognition sites applied on the basis of the known human MCP-1 gene sequence (see, for example, Yoshimura, T. et al. FEBS Letters 1989, 244, 487-493) were used to amplify a cDNA derived from human vascular endothelial cells (purchased from Kurabow) according to a PCR method. The amplified fragment was cleaved with restriction enzymes (PstI and XbaI) and then ligated into a transfer vector pVL1393 (Invitrogen Co.). The resulting vector was co-transfected with an infectious baculovirus into Sf-9 insect cells. Human MCP-1 gene recombinant baculoviruses were isolated from the obtained supernatant by a plaque assay method.

2. Synthesis of [¹²⁵I]-labeled human MCP-1 expressed with baculovirus

[0384] According to the method of Ishii, K. et al. (see Biochemical and Biophysical Research Communications, 1995, 206, 955-961), 5×10^6 cells of Sf-9 insect cells were infected with 5×10^7 PFU (plaque-forming units) of the above human MCP-1 gene recombinant baculoviruses and cultured in EX-CELL 401 medium for 7 days. The resulting culture supernatant was affinity purified by a heparin-Sepharose column (Pharmacia Co.) and then subjected to reverse phase HPLC (Vydac C18 column) to afford a purified human MCP-1. The protein labeling of the resulting purified human MCP-1 was requested for Amersham Co. to obtain a [¹²⁵I]-labeled human MCP-1 expressed with baculovirus (specific activity: 2000 Ci/mmol) prepared by the Bolten Hunter method. The resulting [¹²⁵I]-labeled human MCP-1 was used for the following tests.

3-1. Measurement of inhibitory activity against binding of [¹²⁵I]-labeled human MCP-1 expressed with baculovirus to THP-1 cells (method 1)

[0385] THP-1 cells which are human monocytic leukemia cell line were suspended in an assay buffer [prepared by adding 0.1% of BSA and 25 mM of HEPES to RPMI-1640 (Gibco-BRL Co.) and adjusting the pH to 7.4] so as to provide 1×10^7 cells/mL to thereby afford a cell suspension. A solution obtained by diluting the test compound with the assay buffer was used as a test compound solution. A solution prepared by diluting the above [¹²⁵I]-labeled human MCP-1 expressed with baculovirus with the assay buffer so as to provide 1 μ Ci/mL was used as a labeled ligand solution. In a 96-well filter plate (Millipore Co.), were aliquoted 25 μ L of the test compound solution, 25 μ L of the labeled ligand solution and 50 μ L of the cell suspension in the order mentioned for each well. The solutions were stirred (100 μ L of the reaction solution) and then incubated at 18 °C for 1 hour.

[0386] After completing the reaction, the reaction solution was filtered through a filter, and the filter was washed with 200 μ L of cold PBS twice (the reaction solution was filtered after adding 200 μ L of the cold PBS). The filter was air-dried and 25 μ L of liquid scintillator was then added into each well to count the radioactivity retained by the cells on

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the filter using TopCount (Packard Instrument Co.).

[0387] The count when 100 ng of the above human MCP-1 expressed with baculovirus (unlabeled) instead of the test compound was added was subtracted as nonspecific adsorption, and the count when the test compound was not added was taken as 100%. Thereby, the inhibitory activity of the test compound against binding of the human MCP-1 to THP-1 cells was calculated.

$$\text{Inhibition ratio (\%)} = \{1 - (A - B) / (C - B)\} \times 100$$

(wherein A is the count when the test compound is added; B is the count when 100 ng of the unlabeled human MCP-1 is added; C is the count when only the [¹²⁵I]-labeled human MCP-1 is added).

[0388] When the inhibitory activity of the cyclic amine derivatives which are active ingredients of the present invention was measured, for example, the following compounds respectively manifested an inhibitory activity of 20 to 50%, 50% to 80% and >80% at a concentration of 1 μM, 10 μM or 100 μM.

[0389] Compounds which manifested an inhibitory activity of 20% to 50% at a concentration of 100 μM:

Compd. Nos. 3, 6, 11, 15, 16, 19, 28, 44, 88, 92, 94, 104, 111, 112, 124, 125, 133, 219, 220, 224, 228, 236, 338, 343, 346, 347, 348, 349, 362, 363, 367, 368, 371, 373, 381, 618, 847, 849, 850, 866, 867, 869, 870, 871, 872 and 873

[0390] Compounds which manifested an inhibitory activity of 50% to 80% at a concentration of 100 μM:

Compd. Nos. 1, 8, 10, 12, 18, 21, 26, 30, 33, 35, 39, 84, 89, 90, 91, 96, 97, 98, 99, 100, 101, 103, 106, 108, 109, 110, 116, 122, 126, 216, 218, 221, 225, 226, 231, 330, 332, 333, 334, 337, 341, 342, 350, 352, 354, 356, 359, 360, 361, 364, 366, 374, 375, 379, 382, 462, 463, 464, 557, 686, 840, 841, 842, 843, 844, 845, 846, 848, 862, 863, 864, 865, 868

[0391] Compounds which manifested an inhibitory activity of >80% at a concentration of 100 μM:

Compd. Nos. 2, 4, 5, 7, 13, 14, 17, 20, 22, 23, 24, 25, 27, 29, 31, 32, 34, 36, 38, 40, 41, 42, 43, 45, 46, 47, 48, 49, 50, 83, 85, 86, 95, 102, 105, 107, 113, 114, 115, 119, 120, 121, 123, 127, 128, 129, 130, 131, 132, 134, 214, 215, 217, 227, 237, 238, 331, 335, 336, 339, 340, 345, 351, 355, 357, 358, 383, 458, 459, 460, 466, 558, 851, 852, 861 and 874

[0392] Compounds which manifested an inhibitory activity of 20% to 50% at a concentration of 10 μM:

Compd. Nos. 12, 18, 30, 34, 40, 42, 43, 51, 52, 53, 54, 55, 56, 57, 59, 60, 64, 66, 75, 76, 77, 78, 79, 82, 89, 90, 97, 98, 102, 103, 116, 127, 128, 129, 130, 132, 135, 136, 140, 141, 144, 156, 157, 159, 160, 161, 162, 163, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 178, 179, 190, 191, 192, 195, 197, 200, 202, 203, 204, 205, 208, 233, 234, 235, 239, 240, 241, 242, 243, 245, 247, 249, 250, 255, 263, 264, 269, 274, 278, 279, 282, 306, 316, 317, 323, 324, 380, 404, 409, 433, 446, 448, 449, 451, 470, 471, 473, 476, 479, 486, 488, 489, 497, 498, 499, 501, 504, 507, 508, 509, 510, 512, 514, 516, 519, 527, 530, 532, 542, 545, 560, 563, 564, 565, 566, 568, 569, 572, 573, 574, 575, 578, 583, 584, 586, 587, 589, 590, 599, 600, 601, 603, 606, 612, 613, 620, 621, 622, 624, 625, 627, 629, 630, 632, 634, 636, 637, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 658, 678, 682, 687, 692, 694, 764, 775, 856, 857, 860, 881, 882, 883, 884, 890, 892, 899, 900, 903, 905, 907, 908, 911, 912, 916, 917, 921, 922, 923, 925, 927, 931, 932, 935, 939, 940, 968, 986, 1039, 1041, 1045, 1047, 1062, 1063 and 1083

[0393] Compounds which manifested an inhibitory activity of 50% to 80% at a concentration of 10 μM:

Compd. Nos. 7, 32, 36, 61, 62, 63, 65, 67, 69, 70, 71, 72, 73, 74, 81, 91, 105, 114, 121, 123, 134, 137, 138, 139, 146, 147, 148, 149, 151, 154, 165, 177, 232, 244, 248, 251, 252, 253, 256, 259, 261, 266, 267, 276, 286, 292, 293, 295, 301, 305, 307, 310, 314, 315, 320, 322, 328, 434, 435, 436, 437, 439, 440, 443, 447, 450, 452, 453, 454, 455, 456, 468, 469, 472, 474, 475, 477, 478, 480, 481, 482, 483, 485, 490, 493, 494, 500, 505, 511, 517, 520, 529, 534, 540, 543, 544, 548, 555, 556, 561, 562, 570, 576, 579, 611, 617, 853, 854, 855, 858, 859, 875, 877, 879, 880, 885, 886, 887, 888, 891, 894, 895, 904, 906, 909, 910, 913, 914, 918, 928, 930, 933, 937, 938, 945, 970, 1040, 1044 and 1046

[0394] Compounds which manifested an inhibitory activity of >80% at a concentration of 10 μM:

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Compd. Nos. 31, 45, 46, 48, 58, 68, 80, 83, 113, 115, 142, 143, 145, 150, 152, 265, 268, 272, 275, 283, 285, 287, 288, 290, 291, 294, 296, 297, 302, 308, 309, 313, 321, 325, 326, 358, 438, 441, 442, 444, 445, 457, 466, 467, 484, 487, 491, 492, 495, 496, 503, 518, 537, 538, 547, 554, 876, 878, 919, 929 and 943

5 **[0395]** Compounds which manifested an inhibitory activity of 20% to 50% at a concentration of 1 μ M:

Compd. Nos. 1118, 1121, 1136, 1143, 1146, 1158, 1159, 1167, 1170, 1359, 1361, 1362 and 1363

10 **[0396]** Compounds which manifested an inhibitory activity of 50% to 80% at a concentration of 1 μ M:

Compd. Nos. 1133, 1134, 1137, 1141, 1156, 1161, 1162, 1163, 1164 and 1166

[0397] Compounds which manifested an inhibitory activity of >80% at a concentration of 1 μ M:

15 Compd. No. 1147.

3-2. Measurement of inhibitory activity against binding of [¹²⁵I]-labeled human MCP-1 expressed with baculovirus to THP-1 cells (method 2)

20 **[0398]** THP-1 cells which are human monocytic leukemia cell line were suspended in an assay buffer (containing 50 mM of HEPES, 1.0mM of CaCl₂, 5.0 mM of MgCl₂ and 0.5% of BSA at pH 7.4) so as to provide 1×10⁷ cells/mL to thereby obtain a cell suspension. A solution obtained by diluting the test compound with the assay buffer was used as a test compound solution. A solution prepared by diluting the above [¹²⁵I]-labeled human MCP-1 expressed with baculovirus with the assay buffer so as to provide 1 μ Ci/mL was used as a labeled ligand solution. In a 96-well filter plate (Millipore Co.), were aliquoted 25 μ L of the test compound solution, 25 μ L of the labeled ligand solution and 50 μ L of the cell suspension in the order mentioned for each well. The solutions were stirred (100 μ L of the reaction solution) and then incubated at 18 °C for 1 hour.

25 **[0399]** After completing the reaction, the reaction solution was filtered through a filter, and the filter was washed with 200 μ L of cold PBS twice (the reaction solution was filtered after adding 200 μ L of the cold PBS). The filter was air-dried, and 25 μ L of liquid scintillator was then added by into each well to count the radioactivity retained by the cells on the filter using TopCount (Packard Instrument Co.). The count when 100 ng of the above human MCP-1 expressed with baculovirus(unlabeled) instead of the test compound was added was subtracted as nonspecific adsorption, and the count when the test compound was not added was 100%. Thereby, the inhibitory activity of the test compound against binding of the human MCP-1 to THP-1 cells was calculated.

35

$$\text{Inhibition ratio (\%)} = \{1 - (A - B)/(C - B)\} \times 100$$

40 (wherein A is the count when the test compound is added; B is the count when 100 ng of the unlabeled human MCP-1 is added; C is the count when only the [¹²⁵I]-labeled human MCP-1 is added).

[0400] When the inhibitory activity of the cyclic amine derivatives which are the active ingredients of the present invention was measured, for example, the following compounds respectively manifested an inhibitory activity of 20% to 50%, 50% to 80% and >80% at a concentration of 0.2 μ M, 1 μ M or 10 μ M.

45 **[0401]** Compounds which manifested an inhibitory activity of 20% to 50% at a concentration of 10 μ M:

Compd. No. 1560

[0402] Compounds which manifested an inhibitory activity of 50% to 80% at a concentration of 10 μ M:

50 Compd. No. 1550

[0403] Compounds which manifested an inhibitory activity of >80% at a concentration of 10 μ M:

Compd. Nos. 541, 1042, 1043 and 1559

55

[0404] Compounds which manifested an inhibitory activity of 20% to 50% at a concentration of 1 μ M:

Compd. Nos. 1098, 1100, 1101, 1104, 1105, 1109, 1110, 1116, 1174, 1175, 1176, 1178, 1187, 1188, 1189, 1197,

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1198, 1199, 1200, 1201, 1202, 1209, 1210, 1211, 1212, 1222, 1225, 1229, 1230, 1237, 1238, 1243, 1250, 1259, 1261, 1265, 1266, 1272, 1277, 1282, 1294, 1299, 1302, 1307, 1315, 1318, 1319, 1320, 1329, 1330, 1335, 1336, 1337, 1343, 1344, 1353, 1355, 1356, 1357, 1358, 1368, 1372, 1385, 1386, 1392, 1400, 1413, 1422, 1423, 1425, 1426, 1429, 1430, 1432, 1437, 1440, 1445, 1446, 1447, 1448, 1450, 1452, 1453, 1455, 1458, 1459, 1461, 1463, 1464, 1466, 1468, 1469, 1470, 1471, 1474, 1479, 1482, 1485, 1507, 1508, 1510, 1511, 1512, 1513, 1514, 1515, 1516, 1518, 1519, 1521, 1522, 1524, 1535, 1538, 1540, 1542, 1544, 1571, 1573, 1574, 1575, 1576, 1577, 1578, 1579, 1580, 1581, 1582, 1585, 1587, 1598, 1602, 1603, 1604, 1609, 1611, 1612, 1613, 1614, 1615, 1616, 1617, 1618, 1622, 1627, 1630, 1643, 1646, 1662, 1669, 1716, 1717, 1723, 1728, 1731, 1733, 1736, 1739, 1740, 1747, 1750, 1755, 1757, 1758, 1759, 1760, 1761, 1762, 1769, 1770, 1771, 1772, 1773, 1774, 1777, 1783, 1784, 1785, 1791, 1793, 1904, 1911, 1917, 2057, 2061, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2071, 2072, 2073, 2074, 2075, 2076, 2080, 2081, 2082, 2110, 2112, 2123, 2130, 2131, 2139, 2170, 2180, 2181, 2182, 2212, 2216, 2217, 2219, 2220, 2222, 2224, 2225, 2228, 2247, 2253, 2254, 2255, 2256 and 2257

[0405] Compounds which manifested an inhibitory activity of 50% to 80% at a concentration of 1 μ M:

Compd. Nos. 37, 298, 318, 1084, 1091, 1103, 1106, 1108, 1111, 1113, 1114, 1115, 1138, 1142, 1165, 1179, 1190, 1192, 1193, 1195, 1196, 1204, 1205, 1206, 1207, 1208, 1245, 1246, 1255, 1257, 1258, 1262, 1263, 1293, 1300, 1342, 1351, 1352, 1354, 1370, 1371, 1373, 1375, 1377, 1378, 1380, 1381, 1383, 1384, 1391, 1411, 1412, 1414, 1417, 1418, 1419, 1421, 1424, 1431, 1436, 1439, 1449, 1454, 1456, 1457, 1460, 1462, 1472, 1473, 1487, 1502, 1504, 1506, 1517, 1525, 1526, 1527, 1529, 1530, 1531, 1532, 1533, 1534, 1536, 1537, 1539, 1541, 1545, 1593, 1600, 1601, 1606, 1608, 1619, 1620, 1621, 1623, 1624, 1625, 1626, 1628, 1629, 1645, 1650, 1654, 1658, 1663, 1664, 1665, 1670, 1671, 1672, 1673, 1675, 1678, 1679, 1681, 1684, 1687, 1688, 1689, 1690, 1711, 1712, 1714, 1718, 1722, 1725, 1726, 1727, 1729, 1730, 1732, 1734, 1735, 1737, 1741, 1742, 1743, 1744, 1745, 1746, 1748, 1751, 1753, 1754, 1756, 1779, 1781, 1782, 1786, 1788, 1789, 1790, 1792, 1795, 1797, 1798, 1800, 1801, 1804, 1848, 1862, 1883, 1885, 1886, 1887, 1889, 1893, 1894, 1903, 1905, 1910, 1912, 1913, 1914, 1918, 1922, 1976, 1985, 2027, 2035, 2062, 2083, 2084, 2088, 2089, 2090, 2111, 2124, 2125, 2126, 2135, 2167, 2171, 2175, 2211, 2221, 2226, 2231 and 2240

[0406] Compounds which manifested an inhibitory activity of >80% at a concentration of 1 μ M:

Compd. Nos. 299, 311, 312, 329, 1042, 1043, 1085, 1119, 1191, 1203, 1220, 1228, 1236, 1244, 1256, 1288, 1295, 1308, 1310, 1376, 1382, 1393, 1395, 1415, 1416, 1420, 1435, 1438, 1441, 1480, 1481, 1570, 1583, 1584, 1589, 1590, 1594, 1595, 1607, 1634, 1660, 1661, 1666, 1668, 1695, 1696, 1697, 1698, 1699, 1701, 1702, 1703, 1704, 1705, 1706, 1707, 1708, 1709, 1713, 1724, 1749, 1752, 1775, 1776, 1778, 1780, 1787, 1794, 1796, 1799, 1802, 1803, 1841, 1869, 1870, 1871, 1872, 1876, 1877, 1892, 1896, 1897, 1898, 1899, 1900, 1901, 1902, 1906, 1907, 1908, 1909, 1915, 1916, 1919, 1920, 1921, 2085, 2086, 2087, 2113, 2114, 2118, 2119, 2120, 2121, 2122, 2127, 2128, 2129, 2132, 2133, 2136, 2137, 2138, 2159, 2161, 2162, 2169, 2172, 2178, 2179, 2187, 2189, 2193, 2210, 2213, 2214, 2215, 2218, 2227, 2229, 2230, 2232, 2233, 2235, 2236, 2237, 2238, 2241, 2242, 2243, 2244, 2245, 2246, 2248, 2249, 2250, 2251 and 2252

[0407] Compounds which manifested an inhibitory activity of 20% to 50% at a concentration of 0.2 μ M:

Compd. Nos. 1680, 1682, 1686, 1691, 1694, 1700, 1805, 1810, 1811, 1812, 1813, 1815, 1816, 1817, 1818, 1819, 1820, 1824, 1825, 1826, 1827, 1828, 1832, 1833, 1834, 1835, 1836, 1839, 1840, 1842, 1843, 1851, 1852, 1853, 1854, 1855, 1856, 1858, 1859, 1860, 1863, 1864, 1865, 1866, 1868, 1874, 1878, 1879, 1880, 1888, 1890, 1891, 1895, 1926, 1927, 1928, 1929, 1930, 1934, 1935, 1937, 1945, 1946, 1951, 1952, 1953, 1954, 1959, 1960, 1961, 1962, 1966, 1969, 1970, 1971, 1972, 1973, 1977, 1978, 1979, 1980, 1981, 1985, 2014, 2027, 2028, 2033, 2035, 2039, 2040, 2041, 2042, 2044, 2045 and 2046

[0408] Compounds which manifested an inhibitory activity of 50% to 80% at a concentration of 0.2 μ M:

Compd. Nos. 1677, 1678, 1679, 1681, 1687, 1688, 1689, 1690, 1695, 1697, 1808, 1809, 1841, 1848, 1861, 1862, 1869, 1870, 1871, 1872, 1873, 1876, 1877, 1883, 1884, 1885, 1886, 1887, 1889, 1893, 1894 and 1976

[0409] Compounds which manifested an inhibitory activity of >80% at a concentration of 0.2 μ M:

Compd. Nos. 1696 and 1892.

[Example 2045] Measurement of inhibitory activity against binding of MCP-1 to cells expressing the MCP-1 receptor (Evaluation using [¹²⁵I]-labeled human MCP-1)

1. Obtaining of cells expressing the MCP-1 receptor

[0410] An MCP-1 receptor cDNA fragment obtained by Yamagami, S. et al. (see Biochemical and Biophysical Research Communications, 1994, 202, 1156-1162) was cloned into an NotI site of an expression plasmid pCEP-4 (Invitrogen Co.), and the resulting plasmid was transfected into human kidney epithelial cell line 293-EBNA with a Lipofectamine reagent (Gibco-BRL Co.) and the cells were cultured in the presence of a selective agent (Hygromycin) to provide a stably expressing transfectant line. The expression of the receptor was confirmed by binding properties of the [¹²⁵I]-labeled human MCP-1.

2. Measurement of inhibitory activity against binding of [¹²⁵I]-labeled human MCP-1 expressed with baculovirus to MCP-1 receptor-expressing cells

[0411] The MCP-1 receptor-expressing cells on a tissue culture dish were scraped using a cell scraper and suspended in the assay buffer [prepared by adding 0.1% of BSA and 25 mM of HEPES to D-MEM (Gibco-BRL Co.) and adjusting the pH to 7.4] to thereby provide a cell suspension of a concentration 6×10^6 cells/ml. The same subsequent procedures were performed as described in Example 2044.

[0412] When the inhibitory activity of the cyclic amine derivatives, which were the active ingredients of the present invention, was measured, the inhibitory activity of the representative compounds in the Example was approximately the same as that described in Example 2044.

[Example 2046] Measurement of inhibitory activity against cell chemotaxis

[0413] In order to determine the inhibitory activity of the compounds according to the present invention against the cell chemotaxis, human monocytic leukemia cell line THP-1 were used as chemotactic cells according to the method of Fall et al. (J. Immunol. Methods, 1980, 33, 239-247) to determine the cell chemotaxis caused by monocyte chemotactic factor MCP-1 as follows: Namely, 2×10^6 cells/mL of the THP-1 cells [suspended in RPMI-1640 (Flow Laboratories Co.) + 10% FCS] were placed in the upper chamber (200 μ L) of a 96-well microchemotaxis chamber (Neuroprobe [®]), and human recombinant MCP-1 (Peprtech Co.) diluted with the same solution so as to provide the final concentration of 20 ng/mL was placed in the lower chamber (35 μ L). A polycarbonate filter (PVP-free, Neuroprobe [®]) was placed between the two chambers. These were incubated in the presence of 5% of CO₂ at 37°C for 2 hours.

[0414] The filter was removed, and the cells which had migrated to the undersurface of the filter were immobilized, stained using Diff Quick (Kokusai Shiyaku Co.) and then measured at a measuring wavelength of 550 nm using a plate reader (Molecular Device Co.) to determine the means of 3 wells. Thereby, the indication of the number of cells migrated was obtained. The test compound together with the THP-1 cells was added to the upper chamber at various concentrations to determine the inhibitory activity against cell chemotaxis [degree of inhibition: IC₅₀ (μ M)]. The degree of inhibition was defined as {(number of cells migrated with MCP-1 when no test compound was added to the upper chamber) - (number of cells migrated when no MCP-1 was added to the lower chamber) = 100%}, and the concentration of the compound manifested 50% of the inhibition was designated as IC₅₀.

[0415] When the inhibitory activity of the cyclic amine derivatives which are the active ingredients of the present invention was determined, for example, the IC₅₀ value of the following compounds was 0.1 μ M or below.

[0416] Examples of compounds which manifested an IC₅₀ value of 0.1 μ M or below:

Compd. Nos. 4, 37, 298, 299, 311, 312, 318, 329, 461, 886, 909, 1042, 1043, 1085, 1119, 1138, 1142, 1165, 1179, 1191, 1203, 1205, 1220, 1228, 1236, 1244, 1245, 1256, 1288, 1293, 1295, 1308, 1310, 1352, 1376, 1382, 1393, 1395, 1416, 1420, 1435, 1436, 1438, 1441, 1480, 1531, 1532, 1570, 1583, 1584, 1589, 1590, 1594, 1595, 1600, 1601, 1607, 1660, 1661, 1664, 1666, 1668, 1698, 1699, 1701, 1702, 1703, 1704, 1706, 1707, 1708, 1709, 1713, 1775, 1776, 1778, 1779, 1787, 1794, 1796, 1799, 1802, 1803, 1896, 1898, 1899, 1900, 1901, 1902, 1906, 1907, 1908, 1909, 1915, 1916, 1919, 1920, 1921, 2087, 2114, 2128, 2129, 2132, 2137, 2141, 2144, 2157, 2158, 2189, 2213, 2214, 2235, 2236, 2241, 2242, 2244, 2249, 2250 and 2251

[0417] The results in Examples 2043, 2044, 2045 and 2046 definitely show that the compounds of the present invention as a receptor antagonist of chemokines such as MIP-1 α and/or MCP-1 have the inhibitory activity against actions of the chemokines on target cells.

[Reference Example 2047] Studies on inhibitory effects on collagen-induced arthritis in mice

[0418] Collagen-induced arthritis in mice was induced according to the method of Kato et al. (Arthritis in mice induced by a single immunization with collagen, Ann. Rheum. Dis., 55, 535-539, 1996).

1. Method

[0419] Type II collagen derived from a bovine joint (Collagen Gijutsu-kenshukai) was emulsified with an volume of a Freund's complete adjuvant (ICN Immunobiologicals) to prepare a homogeneous emulsion. An ultrasonic homogenizer (Taitec) was used to prepare the emulsion. The emulsion (in a dose of 0.15 mg/0.1 mL/body) was intracutaneously injected into the base of the tail of DBA/1 mice (Charles River, Japan Inc.) by using a glass syringe for tuberculin and a 27G injection needle.

[0420] The test compound was suspended in a 0.5% aqueous solution of sodium carboxymethyl cellulose (CMC, Wako Pure Chemical Industries, Ltd.) with a mortar to prepare a prescribed administration suspension, which was orally administered from the date after the administration of the emulsion.

[0421] The experimental groups are three of a group administered with 0.5% of CMC (hereinafter referred to as the control group) and groups administered with 30 mg/kg or 100 mg/kg of the test compound. The solution or the test compound was administered once a day, and the number of animals in each group was 16.

2. Evaluation of arthritis

[0422] The degree of joint swelling was scored for each digital joint of four limbs after the passage of 12 weeks from the administration of the emulsion according to the method of Abe (immunotherapy in arthritis model, Japanese Journal of Inflammations 12, 417-422, 1992). Each limb was scored in four grades of scores 0 to 3, and the maximum was score 12.

3. Actions on synovial hyperplasia, chondrolysis of articular cartilages and osteolysis of subchondral bone

[0423] After observing the arthritis scores, the right hindlimbs were removed. After embedding in paraffin, thin slice of knee joint were prepared and subjected to hematoxylin-eosin staining to evaluate actions on synovial hyperplasia, chondrolysis, destruction of articular cartilages and osteolysis of subchondral bone according to a conventional method. The rating was carried out in five grades of scores 0 to 4 for each measurement item.

4. Results of evaluation

[0424] The category type Dunnett's tests compared with the control group were carried out, and a p value of 0.05 or below was taken as significantly different. The following graphs are expressed as mean \pm standard deviation (SD). Fig. 1 illustrates the results of arthritis when Compd. No. 1583 was orally administered for 12 weeks. The group administered with Compd. No. 1583 significantly inhibited arthritis scores as compared with the control group.

[0425] Figs. 2 to 4 respectively illustrates results of Compd. No.1583 on synovial hyperplasia, chondrolysis of articular cartilages and osteolysis of subchondral bone. Compd. No.1583 significantly inhibited for all the evaluation items.

[Reference Example 2048] Studies on inhibitory effects on collagen-induced arthritis in rats

[0426] Collagen-induced arthritis in rats was induced by modifying the method of Trentham et al. (Autoimmunity to type II collagen: an experimental model of arthritis. J. Exp. Med., 146, 857-68 (1977) as follows:

1. Method

[0427] Type II collagen derived from a bovine joint (Collagen Gijutsu-kenshukai) and muramyl dipeptide (CHEMICON International) were mixed with an Freund's incomplete adjuvant so as to provide each final concentration of 0.08% and 0.02% to thereby prepare a homogenous emulsion. The resulting emulsion was prepared by vigorous stirring at 4 °C in two glass syringes connected with a connector. One mL of the emulsion was injected intradermally in 10 sites on the back of Lewis female rats (Charles River Japan, Inc., 6-weeks-old) by using a glass syringe for tuberculin and a 26G injection needle. After one week, the base of the tail was additionally immunized (boosted) intradermally with 0.1 mL of the emulsion prepared by the same method as described above.

[0428] The test compound was suspended in a 0.5 % aqueous solution of sodium carboxymethylcellulose (CMC, Wako Pure Chemical Industries, Ltd.) with a mortar to prepare a prescribed administration suspension, which was

orally administered every day for 3 weeks after the date of the initial administration of the emulsion.

[0429] The experimental groups were a group of no treatment (intact group), a group administered with 0.5% of the CMC (hereinafter referred to as the control group) and a group administered with 300 mg/kg of Compd. No. 1245. The solution or the test compound was administered once a day. The number of animals in each group was 8.

2. Evaluation of arthritis

[0430] The limb joint swelling of hindlimbs was evaluated by determining a change in the volume of the limb joints. The footpad volumes of the right and left hindlimbs of rats were measured total 7 times of the date of boosting, 2, 5, 7, 9, 12 and 14 days after the date of boosting by using a rat hindlimb footpad volume meter (TK-105, UNICON). The obtained results were expressed as an increasing rate after the date of boosting by taking the footpad volume on the Co., Ltd.) using a Hitachi 7070 model autoanalyzer.

[0431] The test compound was daily orally administered in a dose of 100 mg/kg body weight twice a day from the date of injecting the anti-glomerular basement membrane serum (about 10:00 a.m. and about 6:00p.m. in Experiment 1 and about 10:00 a.m. and about 5:00 p.m. in Experiment 2). In the control group, only the solution (a 0.5% aqueous solution of sodium carboxymethylcellulose) was orally administered. The administration volume was 10 mL/kg body weight, and the number of animals (N) was 10.

2. Results and Discussion

[0432] The detection of proteinuria began in each experimental group on the 4th day after injecting the anti-glomerular basement membrane serum, and the concentration of the urinary proteins was subsequently increased to the 14th day with time to induce nephritis. In the group administered with Compd. No. 1583, a tendency to inhibit the concentration of urinary proteins by 26% was found as compared with the control group on the 7th day after injecting the antiserum. A significant inhibition of the concentration of urinary proteins was found by 51 and 54% on the 10th and 14th days ($p<0.01$, Mann-Whitney U test). (Fig. 6). When the creatinine concentration in blood was measured on the 15th day after injecting the anti-glomerular basement membrane serum, a significant decrease of 20% ($p<0.01$, Mann-Whitney U test) was found in the group administered with Compd. No. 1583 as compared with the control group (Table 53).

[0433] Therefore, it is found that the glomerular injury and renal function exacerbation of rats were alleviated with Compd. No. 1583 to inhibit nephritis.

Table 53

Inhibitory Effects on Serum Creatinine Serum Creatinine Concentration (mg/dl) on the 15th Day of Administering Compound	
Placebo	Compd. No. 1583
0.49±0.06	0.39±0.03**

2-2. Experiment 2

[0434] The detection of proteinuria began in each experimental group on about date of boosting as 100%. The mean of the group was obtained as the mean of all the left and right hindlimb volumes in each group.

3. Results of evaluation

[0435] Fig. 5 illustrates results of arthritis when Compd. No. 1245 was orally administered every day for 3 weeks. Values in the figure are expressed as mean ± S.E. Student's t-tests or Wilcoxon tests were carried out comparing with the control group, and a P value of 0.05 or below was taken as significantly different. The group administered with Compd. No. 1245 significantly inhibited joint swelling (after 5, 7 and 14 days: $P<0.01$ and after 9 and 12 days: $P<0.001$) as compared with the control group at each time point of 5, 7, 9, 12 and 14 days after the boosting.

[0436] The results of Examples 2047 and 2048 show that the compounds of the present invention have effective remedial or prophylactic effects on diseases in association with chondrolysis of cartilage or osteolysis such as arthritis, rheumatoid arthritis, osteoarthritis, traumatic articular destruction, osteoporosis or tumor.

[Example 2049] Studies on inhibitory actions in Masugi's nephritis model in WKY-rats

1. Method (common to Experiments 1 and 2)

[0437] Rabbits were immunized with a trypsin fraction of rat kidney cortex to provide an anti-glomerular basement membrane serum which was intravenously injected to 4-weeks-old female WKY rats (Charles River) in a dose of 2.5 mL/kg body weight to induce glomerulonephritis.

[0438] After injection of the antiserum, urine of each animal was collected for 24 hours with metabolic cages for rats (Clea Japan, Inc.) on the 1st, 4th, 7th, 10th and 14th days after the injection. The amount of the urine was measured by urine weight and the protein content in the urine was measured by using a kit for assaying proteins in urine and cerebrospinal fluid (Tonein TP-II, Otsuka Pharmaceutical Co., Ltd.) to determine the amount of proteins excreted in urine per day.

[0439] Serum of the animals subjected to the experiments was collected on the 15th day after injecting the antiserum, and creatinine concentration in blood was measured with a creatinine assay kit (Autosera ®, Daiichi Pure Chemicals the 4th day after injecting the anti-glomerular basement membrane serum, and the concentration of the urinary proteins was subsequently increased to the 14th day with time to confirm the induction of nephritis. In the group administered with Compd. No.1245, a significant ($p<0.001$, Mann-Whitney U test) inhibition of the concentration of urinary proteins was respectively found by 74, 85, 81 and 82% on the 4th, 7th, 10th and 14th days after injecting the antiserum as compared with the control group (Fig. 7). When the creatinine concentration in blood was measured on the 15th day after injecting the anti-glomerular basement membrane serum, a significant decrease of 10% ($p<0.05$, Student's t-test) was found in the group administered with compound 1245 as compared with the control group (Table 54).

[0440] Therefore, it is found that the glomular injury and renal function exacerbation of rats were alleviated with Compd. No. 1245 to inhibit nephritis.

Table 54

Inhibitory Effects on Serum Creatinine Serum Creatinine Concentration (mg/dl) on the 15th Day of Administering Compd. No. 1245	
Control	Compd. No. 1245
0.53±0.05	0.48±0.04

[0441] The above results show that the compound of the present invention has effective remedial or prophylactic effects on nephritis or nephropathy such as glomerulonephritis, interstitial nephritis or nephrotic syndrome.

[Reference Example 2050] Studies on inhibitory effects in chronic relapsing experimental allergic encephalomyelitis in mice

1. Method

[0442] Animal models of chronic recurrent experimental allergic encephalomyelitis were prepared according to the method described in the report by Okuda et al. [Okuda Y., et al. J. Neuroimmunol. 81, 201-210 (1998)].

[0443] Into the abdomen of 8-weeks-old female SJL/J×PL/J F1 mice (Jackson Lab.), were subcutaneously injected 100 µL of an emulsion of an Freund's incomplete adjuvant (Diffco) containing 500 µg of rabbit myelin basic protein (Sigma) and 500 µg of Mycobacterium tuberculosis H37Ra (Difco)/isotonic sodium chloride solution = 1:1 (volume ratio). After 24 hours, 100 µL of isotonic sodium chloride solution containing 400 ng of Bordetella pertussis toxin (Sigma) was intraperitoneally injected to induce the chronic relapsing experimental allergic encephalomyelitis. The number of animals in each group was 10.

[0444] The test compound was suspended in a 0.5% (weight/volume) aqueous solution of sodium carboxymethyl-cellulose (Wako Pure Chemical Industries, Ltd.) with a mortar to prepare a prescribed suspension, which was orally administered from the date of injection of the emulsion.

[0445] Clinical symptoms of the chronic relapsing experimental allergic encephalomyelitis were evaluated by observation on animal individuals once a day by using the method described by Tahira et al. ["Methods of Immunological Experimental Procedures" p. 1178-1181, Nankodo (1995)]. Namely, score 0 = normal; score 1 = limp tail; score 2 = slight walking abnormality; score 3 = apparent hindlimb paresis; score 4 = complete hindlimb paralysis and score 5 = moribund or death.

2. Results and Discussion

2-1. Experiment 1: Effects of Compd. No. 1583

[0446] Table 55 and Fig. 8 show the results to 41 days after injection of the emulsion.

[0447] The change in symptoms was expressed by means of the respective experimental groups on each observation day. In the maximal clinical scores in Table 55, the maximal value of the clinical scores shown in the observation period by the respective animals were adopted as the representative scores of the example. As to statistical analytical methods, nonparametric tests among some groups without comparison with to the control group were used for clinical scores and multiple comparisons with the control group (Dunnett's multiple comparison) were used for other evaluation items.

[0448] A tendency to delay the onset date (no significant difference), symptom inhibition ($p < 0.05$) and shortening of onset period ($p < 0.05$) were found at the first attack in the group administered with 100 mg/kg body weight of Compd. No.1583 as compared with the control group. In the group administered with 30 mg/kg body weight of Compd. No. 1583, distinct effects on the items were not found; however, the tendency of dose-dependent effects was found. In Fig. 8, "compound 1" is not Compd. No. 1 in the present invention, but means the compound of Compd. No. 1583.

Table 55

Experimental Group	Control Group	Compd. No. 1583 30 mg/kg body weight	Compd. No. 1583 100 mg/kg body weight
First Attack			
Onset Date	12.6±1.9	12.3±1.9	13.6±2.0
Maximal Clinical Score	3.9±0.6	3.5±0.9	2.4±1.3*
Duration of Clinical Sign	8.8±2.5	9.8±3.3	5.7±3.8*
Second Attack (Relapse)			
Onset Date	26.8±7.5	26.3±3.4	28.5±4.7*
Maximal Clinical Score	3.8±0.8	3.7±0.6	3.0±0.9*
Duration of Clinical Sign	Not calculated	Not calculated	Not calculated

Note: *: $p < 0.05$

2-2. Experiment 2: Effects of Compd. No. 1245

[0449] Table 56 and Fig. 9 illustrate the results to 21 days after injection of the emulsion.

[0450] The change in symptoms was expressed as means of the respective experimental groups on each observation day. As to the maximal clinical scores in Table 56, the maximal values of clinical scores manifested by the respective animals during the observation period were adopted as representative scores of the example. As to statistical analytical methods, nonparametric tests between two groups without comparison with to the control group were used for clinical scores and two group comparison with the control group (Student's t-tests) was used for the other evaluation items.

[0451] The delay in onset date ($p < 0.05$) and a tendency to inhibit symptoms (no significant difference) were found in the group administered with 300 mg/kg body weight of Compd. No. 1245 as compared with the control group.

Table 56

Experimental Group	Control Group	Compd. No. 1245 300 mg/kg body weight
Incidence (Number of Onset Animals/Number of Immunized Animals)	34/39	17/19
Onset Date	11.2±2.0	13.2±2.4*
Maximal Clinical Score	3.0±0.9	2.5±1.5
Duration of Clinical Sign	5.5±1.7	5.4±2.4

* $p < 0.05$

[0452] The above results show that the compound of the present invention has effective remedial or prophylactic effects on demyelinating diseases such as multiple sclerosis.

[0453] The results shown in Examples 2043 to 2050 reveal that the compound of the present invention as a chemokine receptor antagonist can be useful as remedies or prophylactics for various diseases considered to be associated with chemokines such as MIP-1 α and/or MCP-1 such as glomerulonephritis, interstitial nephritis and nephrotic syndrome.

[Example 2051] Production of Tablets

[0454] A tablet containing 30 mg of Compd. No. 1583 was prepared according to the following prescription:

Compd. No. 1583	30 mg
Lactose	87 mg
Starch	30 mg
Magnesium stearate	3 mg

[Example 2052] Production of Parenteral Injection

[0455] Solutions for injection containing 0.3 mg of hydrochloride of Compd. No. 1583 in 1 mL were prepared according to the following prescription:

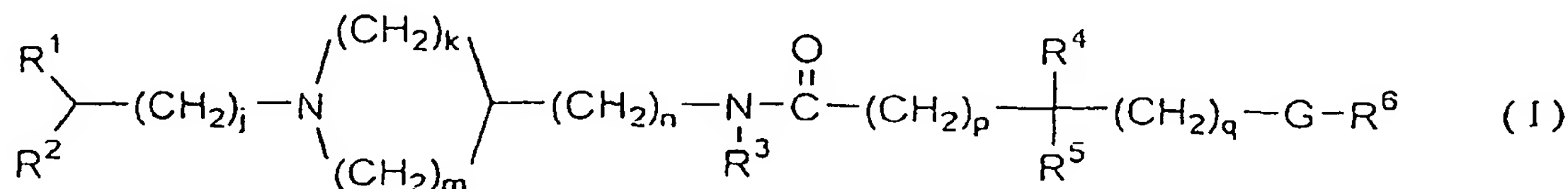
Compd. No. 1583 (hydrochloride)	30 mg
Sodium chloride	900 mg
Distilled water for injection	100 mL

Industrial Applicability

[0456] Cyclic amine compounds used in the present invention, pharmaceutically acceptable acid addition salts thereof or pharmaceutically acceptable C₁-C₆ alkyl addition salts thereof as a chemokine receptor antagonist have inhibitory activities on actions of chemokines such as MIP-1 α and/or MCP-1 on target cells. Therefore, the cyclic amine compounds, pharmaceutically acceptable acid addition salts thereof or pharmaceutically acceptable C₁-C₆ alkyl addition salts thereof are useful as remedies and/or prophylactics for glomerulonephritis, interstitial nephritis and nephrotic syndrome.

Claims

1. Use of a compound according to formula (I), or a pharmaceutically acceptable acid addition salt thereof or pharmaceutically acceptable C₁-C₆ alkyl addition salt thereof, in the manufacture of a medicament for the treatment of glomerulonephritis, interstitial nephritis or nephrotic syndrome;



wherein R¹ is a phenyl group, a C₃-C₈ cycloalkyl group or an aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms; the phenyl group or the aromatic heterocyclic group in the above R¹ may be condensed with a benzene ring or an aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms to form a condensed ring; the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic group or the condensed ring in the above R¹ may be substituted with an optional number of halogen atoms, hydroxy groups, cyano groups, nitro groups, carboxy groups, carbamoyl groups, C₁-C₆ alkyl groups, C₃-C₈ cycloalkyl groups, C₂-C₆ alkenyl groups, C₁-C₆ alkoxy groups, C₁-C₆ alkylthio groups, C₃-C₅ alkylene groups, C₂-C₄ alkyleneoxy groups, C₁-C₃ alkylenedioxy groups, phenyl groups, phenoxy

groups, phenylthio groups, benzyl groups, benzyloxy groups, benzoylamino groups, C₂-C₇ alkanoyl groups, C₂-C₇ alkoxy carbonyl groups, C₂-C₇ alkanoyloxy groups, C₂-C₇ alkanoylamino groups, C₂-C₇ N-alkylcarbamoyl groups, C₄-C₉ N-cycloalkylcarbamoyl groups, C₁-C₆ alkylsulfonyl groups, C₃-C₈ (alkoxy carbonyl)methyl groups, N-phenylcarbamoyl groups, piperidinocarbonyl groups, morpholinocarbonyl groups, 1-pyrrolidinylcarbonyl groups, bivalent groups represented by the formula: NH(C=O)O-, bivalent groups represented by the formula: -NH(C=S)O-, amino groups, mono(C₁-C₆ alkyl)amino groups or di(C₁-C₆ alkyl)amino groups; the substituents of the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic group or the condensed ring may further be substituted with an optional number of halogen atoms, hydroxy groups, amino groups, trifluoromethyl groups, C₁-C₆ alkyl groups or C₁-C₆ alkoxy groups;

R² is a hydrogen atom, a C₁-C₆ alkyl group, a C₂-C₇ alkoxy carbonyl group, a hydroxy group or a phenyl group; the C₁-C₆ alkyl group or the phenyl group in the R² may be substituted with an optional number of halogen atoms, hydroxy groups, C₁-C₆ alkyl groups or C₁-C₆ alkoxy groups, with the proviso that R² is not a hydroxy group when j is 0;

j is an integer of 0 to 2;

k is an integer of 0 to 2;

m is an integer of 2 to 4;

n is 0 or 1;

R³ is a hydrogen atom or a C₁-C₆ alkyl group (which may be substituted with one or two phenyl groups which may respectively be substituted with an optional number of the same or different halogen atoms, hydroxy groups, C₁-C₆ alkyl groups or C₁-C₆ alkoxy groups);

R⁴ and R⁵ are the same or different and are each a hydrogen atom, a hydroxy group, a phenyl group or a C₁-C₆ alkyl group; the C₁-C₆ alkyl group in the R⁴ and R⁵ may be substituted with an optional number of halogen atoms, hydroxy groups, cyano groups, nitro groups, carboxy groups, carbamoyl groups, mercapto groups, guanidino groups, C₃-C₈ cycloalkyl groups, C₁-C₆ alkoxy groups, C₁-C₆ alkylthio groups, phenyl groups (which may be substituted with an optional number of halogen atoms, hydroxy groups, C₁-C₆ alkyl groups, C₁-C₆ alkoxy groups or benzyloxy groups), phenoxy groups, benzyloxy groups, benzyloxycarbonyl groups, C₂-C₇ alkanoyl groups, C₂-C₇ alkoxy carbonyl groups, C₂-C₇ alkanoyloxy groups, C₂-C₇ alkanoylamino groups, C₂-C₇ N-alkylcarbamoyl groups, C₁-C₆ alkylsulfonyl groups, amino groups, mono(C₁-C₆ alkyl)amino groups, di(C₁-C₆ alkyl)amino groups or aromatic heterocyclic groups (having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms) or condensed rings formed by condensation of the aromatic heterocyclic groups (having the 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as the heteroatoms) with benzene rings or both R⁴ and R⁵ together may form a 3- to a 6-membered cyclic hydrocarbon;

p is 0 or 1;

q is 0 or 1;

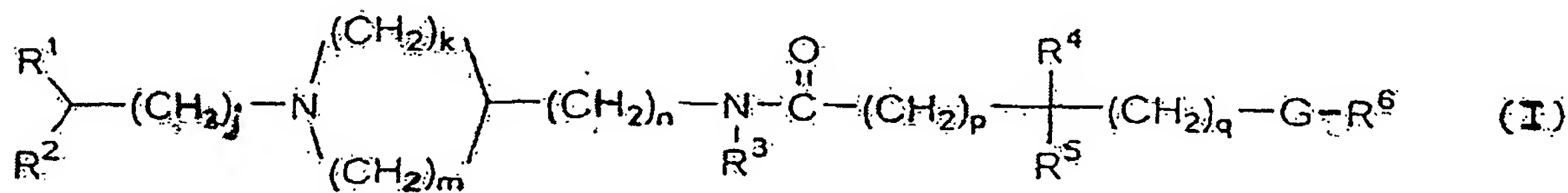
G is a group represented by -CO-, -SO₂-, -CO-O-, -NR⁷-CO-, -CO-NR⁷-, -NH-CO-NH-, -NH-CS-NH-, -NR⁷-SO₂-, -SO₂-NR⁷-, -NH-CO-O- or -O-CO-NH-, wherein R⁷ is a hydrogen atom or a C₁-C₆ alkyl group or R⁷, together with R⁵, may form a C₂-C₅ alkylene group;

R⁶ is a phenyl group, a C₃-C₈ cycloalkyl group, a C₃-C₆ cycloalkenyl group, a benzyl group or an aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms; the phenyl group, the benzyl group or the aromatic heterocyclic group in the R⁶ may be condensed with a benzene ring or an aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms to form a condensed ring; the phenyl group, the C₃-C₈ cycloalkyl group, the C₃-C₆ cycloalkenyl group, the benzyl group, the aromatic heterocyclic group or the condensed ring in the above R⁶ may further be substituted with an optional number of halogen atoms, hydroxy groups, mercapto groups, cyano groups, nitro groups, thiocyanato groups, carboxy groups, carbamoyl groups, trifluoromethyl groups, C₁-C₆ alkyl groups, C₃-C₈ cycloalkyl groups, C₂-C₆ alkenyl groups, C₁-C₆ alkoxy groups, C₃-C₈ cycloalkyloxy groups, C₁-C₆ alkylthio groups, C₁-C₃ alkylene-dioxy groups, phenyl groups, phenoxy groups, phenylamino groups, benzyl groups, benzoyl groups, phenylsulfinyl groups, phenylsulfonyl groups, 3-phenylureido groups, C₂-C₇ alkanoyl groups, C₂-C₇ alkoxy carbonyl groups, C₂-C₇ alkanoyloxy groups, C₂-C₇ alkanoylamino groups, C₂-C₇ N-alkylcarbamoyl groups, C₁-C₆ alkylsulfonyl groups, phenylcarbamoyl groups, N,N-di(C₁-C₆ alkyl)sulfamoyl groups, amino groups, mono(C₁-C₆ alkyl)amino groups, di(C₁-C₆ alkyl)amino groups, benzylamino groups, C₂-C₇ (alkoxy carbonyl)amino groups, C₁-C₆ (alkylsulfonyl)amino groups or bis(C₁-C₆ alkylsulfonyl)amino groups; the substituents of the phenyl group, the C₃-C₈ cycloalkyl group, the C₃-C₆ cycloalkenyl group, the benzyl group, the aromatic heterocyclic group or the condensed ring may further be substituted with an optional number of halogen atoms, cyano groups, hydroxy groups, amino groups, trifluoromethyl groups, C₁-C₆ alkyl groups,

C₁-C₆ alkoxy groups, C₁-C₆ alkylthio groups, mono(C₁-C₆ alkyl)amino groups or di(C₁-C₆ alkyl)amino groups.

Patentansprüche

1. Verwendung einer Verbindung gemäß der Formel (I) oder eines pharmazeutisch geeigneten Säureadditionssalzes hiervon oder eines pharmazeutisch geeigneten C₁-C₆-Alkyladditionssalzes hiervon bei der Herstellung eines Medikaments für die Behandlung von Glomerulonephritis, interstitieller Nephritis oder nephrotischem Syndrom;



worin R¹ eine Phenylgruppe, eine C₃-C₈-Cycloalkylgruppe oder eine aromatische heterozyklische Gruppe mit 1 bis 3 Sauerstoffatomen, Schwefelatomen und/oder Stickstoffatomen als Heteroatomen darstellt; worin die Phenylgruppe oder die aromatische heterozyklische Gruppe in der obigen Gruppe R¹ mit einem Benzolring oder einer aromatischen heterozyklischen Gruppe mit 1 bis 3 Sauerstoffatomen, Schwefelatomen und/oder Stickstoffatomen als Heteroatome unter Bildung eines kondensierten Ringes kondensiert sein kann; worin die Phenylgruppe, die C₃-C₈-Cycloalkylgruppe, die aromatische heterozyklische Gruppe oder der kondensierte Ring in der vorgenannten Gruppe R¹ substituiert sein kann mit einer optionalen Zahl an Halogenatomen, Hydroxygruppen, Cyanogruppen, Nitrogruppen, Carboxygruppen, Carbamoylgruppen, C₁-C₆-Alkylgruppen, C₃-C₈-Cycloalkylgruppen, C₂-C₆-Alkenylgruppen, C₁-C₆-Alkoxygruppen, C₁-C₆-Alkylthiogruppen, C₃-C₅-Alkylengruppen, C₂-C₄-Alkylenoxygruppen, C₁-C₃-Alkylendioxygruppen, Phenylgruppen, Phenoxygruppen, Phenylthiogruppen, Benzylgruppen, Benzyloxygruppen, Benzoylaminogruppen, C₂-C₇-Alkanoylgruppen, C₂-C₇-Alkoxy-carbonylgruppen, C₂-C₇-Alkanoyloxygruppen, C₂-C₇-Alkanoylaminogruppen, C₂-C₇-N-Alkylcarbamoylgruppen, C₄-C₉-N-Cycloalkylcarbamoylgruppen, C₁-C₆-Alkylsulfonylgruppen, C₃-C₈-(Alkoxy-carbonyl)methylgruppen, N-Phenylcarbamoylgruppen, Piperidinocarbonylgruppen, Morpholinocarbonylgruppen, 1-Pyrrolidinylcarbonylgruppen, bivalenten Gruppen, die durch die Formel -NH(C=O)O- repräsentiert sind, bivalenten Gruppen, die durch die Formel -NH(C=S)O- repräsentiert sind, Aminogruppen, Mono-(C₁-C₆-alkyl)aminogruppen oder Di-(C₁-C₆-alkyl)aminogruppen; worin die Substituenten der Phenylgruppe, der C₃-C₈-Cycloalkylgruppe, der aromatischen heterozyklischen Gruppe oder des kondensierten Rings weiterhin substituiert sein können mit einer optionalen Zahl an Halogenatomen, Hydroxygruppen, Aminogruppen, Trifluoromethylgruppen, C₁-C₆-Alkylgruppen oder C₁-C₆-Alkoxygruppen;

worin R² ein Wasserstoffatom, eine C₁-C₆-Alkylgruppe, eine C₂-C₇-Alkoxy-carbonylgruppe, eine Hydroxygruppe oder eine Phenylgruppe repräsentiert; worin die C₁-C₆-Alkylgruppe oder die Phenylgruppe in der Gruppe R² substituiert sein können mit einer optionalen Zahl an Halogenatomen, Hydroxygruppen, C₁-C₆-Alkylgruppen oder C₁-C₆-Alkoxygruppen, unter der Bedingung, dass R² keine Hydroxygruppe ist, wenn j gleich 0 ist;

worin j eine ganze Zahl von 0 bis 2 repräsentiert;

worin k eine ganze Zahl von 0 bis 2 repräsentiert;

worin m eine ganze Zahl von 2 bis 4 repräsentiert;

worin n gleich 0 oder 1 ist;

worin R³ ein Wasserstoffatom oder eine C₁-C₆-Alkylgruppe repräsentiert, (welche substituiert sein kann mit einer oder zwei Phenylgruppen, welche jeweils wiederum substituiert sein können mit einer optionalen Zahl derselben oder verschiedener Halogenatome, Hydroxygruppen, C₁-C₆-Alkylgruppen oder C₁-C₆-Alkoxygruppen);

worin R⁴ und R⁵ gleich oder verschieden sein können und jeweils ein Wasserstoffatom, eine Hydroxygruppe, eine Phenylgruppe oder eine C₁-C₆-Alkylgruppe repräsentieren; worin die C₁-C₆-Alkylgruppe in den Gruppen R⁴ und R⁵ substituiert sein kann mit einer optionalen Zahl an Halogenatomen, Hydroxygruppen, Cyanogruppen, Nitrogruppen, Carboxygruppen, Carbamoylgruppen, Mercaptogruppen, Guanidinogruppen, C₃-C₈-Cycloalkylgruppen, C₁-C₆-Alkoxygruppen, C₁-C₆-Alkylthiogruppen, Phenylgruppen, (welche substituiert sein können mit einer optionalen Zahl an Halogenatomen, Hydroxygruppen, C₁-C₆-Alkylgruppen, C₁-C₆-Alkoxygruppen oder Benzyloxygruppen), Phenoxygruppen, Benzyloxygruppen, Benzyloxycarbonylgruppen, C₂-C₇-Alkanoylgruppen, C₂-C₇-Alkoxy-carbonylgruppen, C₂-C₇-Alkanoyloxygruppen, C₂-C₇-Alkanoylaminogruppen, C₂-C₇-N-Alkylcarbamoylgruppen, C₁-C₆-Alkylsulfonylgruppen, Aminogruppen, Mono-(C₁-C₆-alkyl)aminogruppen, Di-(C₁-C₆-alkyl)aminogruppen oder aromatische heterozyklischen Gruppen (mit 1 bis 3 Sauerstoffatomen, Schwefelatomen und/oder Stickstoffatomen als Heteroatome) oder kondensierten Ringen, die durch die Kondensation der aromatischen heterozyklischen Gruppen (mit 1 bis 3 Sauerstoffatomen, Schwefelatomen und/oder Stickstoffatomen als Heteroatome) mit den Benzolringen gebildet werden oder worin beide R⁴ und R⁵ zusammen einen 3- bis 6-gliedrigen zyklischen Kohlenwasserstoff bilden;

worin p gleich 0 oder 1 ist;

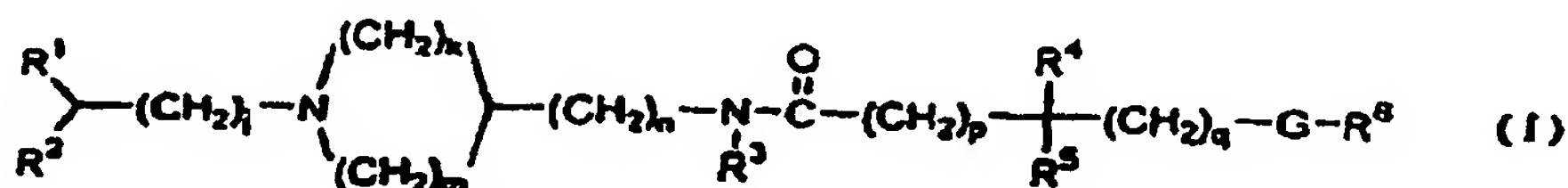
worin q gleich 0 oder 1 ist;

worin G eine Gruppe repräsentiert aus -CO-, -SO₂-, -CO-O-, -NR⁷-CO-, -CO-NR⁷-, -NH-CO-NH-, -NH-CS-NH-, -NR⁷-SO₂-, -SO₂-NR⁷-, -NH-CO-O- oder -O-CO-NH-, worin R⁷ ein Wasserstoffatom oder eine C₁-C₆-Akylgruppe repräsentiert oder worin R⁷ zusammen mit R⁵ eine C₂-C₅-Alkylengruppe bilden kann;

worin R⁶ eine Phenylgruppe, eine C₃-C₈-Cycloalkylgruppe, eine C₃-C₆-Cycloalkenylgruppe, eine Benzylgruppe oder eine aromatische heterozyklische Gruppe mit 1 bis 3 Sauerstoffatomen, Schwefelatomen und/oder Stickstoffatomen als Heteroatome repräsentiert; wobei die Phenylgruppe, die Benzylgruppe oder die aromatische heterozyklische Gruppe in der Gruppe R⁶ mit einem Benzolring oder einer aromatischen heterozyklischen Gruppe mit 1 bis 3 Sauerstoffatomen, Schwefelatomen und/oder Stickstoffatomen als Heteroatome kondensiert sein kann, um einen kondensierten Ring zu bilden; wobei die Phenylgruppe, die C₃-C₈-Cycloalkylgruppe, die C₃-C₆-Cycloalkenylgruppe, die Benzylgruppe, die aromatische heterozyklische Gruppe oder der kondensierte Ring in der vorgenannten R⁶-Gruppe ferner substituiert sein können mit einer optionalen Zahl an Halogenatomen, Hydroxygruppen, Mercaptogruppen, Cyanogruppen, Nitrogruppen, Thiocyanatogruppen, Carboxygruppen, Carbamoylgruppen, Trifluoromethylgruppen, C₁-C₆-Alkylgruppen, C₃-C₈-Cycloalkylgruppen, C₂-C₆-Alkenylgruppen, C₁-C₆-Alkoxygruppen, C₃-C₈-Cycloalkoxygruppen, C₁-C₆-Alkylthiogruppen, C₁-C₈-Alkylendioxygruppen, Phenylgruppen, Phenoxygruppen, Phenylaminogruppen, Benzylgruppen, Benzoylgruppen, Phenylsulfinylgruppen, Phenylsulfonylgruppen, 3-Phenylharnstoffgruppen, C₂-C₇-Alkanoylgruppen, C₂-C₇-Alkoxy-carbonylgruppen, C₂-C₇-Alkanoyloxygruppen, C₂-C₇-Alkanoylaminogruppen, C₂-C₇-N-Alkylcarbamoylgruppen, C₁-C₆-Alkylsulfonylgruppen, Phenylcarbamoylgruppen, N,N-Di-(C₁-C₆-alkyl)sulfamoylgruppen, Aminogruppen, Mono-(C₁-C₆-alkyl)aminogruppen, Di-(C₁-C₆-alkyl)aminogruppen, Benzylaminogruppen, C₂-C₇-(Alkoxy-carbonyl)aminogruppen, C₁-C₆-(Alkylsulfonyl)aminogruppen oder Bis-(C₁-C₆-alkylsulfonyl)aminogruppen; wobei die Substituenten der Phenylgruppe, der C₃-C₈-Cycloalkylgruppe, der C₃-C₈-Cycloalkenylgruppe, der Benzylgruppe, der aromatischen heterozyklischen Gruppe oder des kondensierten Rings ferner substituiert sein können mit einer optionalen Zahl an Halogenatomen, Cyanogruppen, Hydroxygruppen, Aminogruppen, Trifluoromethylgruppen, C₁-C₆-Alkylgruppen, C₁-C₆-Alkoxygruppen, C₁-C₆-Alkylthiogruppen, Mono-(C₁-C₆-alkyl)-aminogruppen oder Di-(C₁-C₆-alkyl)aminogruppen.

Revendications

1. Utilisation d'un composé selon la formule (I), ou d'un sel d'addition d'acide pharmaceutiquement acceptable de celui-ci ou d'un sel d'addition d'alkyle en C₁-C₆ pharmaceutiquement acceptable de celui-ci, pour la fabrication d'un médicament destiné au traitement de la glomérulonéphrite, de la néphrite interstitielle ou du syndrome néphrotique ;



dans laquelle R¹ est un groupe phényle, un groupe cycloalkyle en C₃-C₈ ou un groupe hétérocyclique aromatique ayant de 1 à 3 atomes d'oxygène, atomes de soufre et/ou atomes d'azote en tant qu'hétéroatomes ; le groupe phényle ou le groupe hétérocyclique aromatique dans R¹ ci-dessus peuvent être condensés avec un cycle benzène ou un groupe hétérocyclique aromatique ayant de 1 à 3 atomes d'oxygène, atomes de soufre et/ou atomes d'azote en tant qu'hétéroatomes pour former un cycle condensé ; le groupe phényle, le groupe cycloalkyle en C₃-C₈, le groupe hétérocyclique aromatique ou le cycle condensé dans R¹ ci-dessus peuvent être substitués par un nombre facultatif d'atomes d'halogène, de groupes hydroxy, de groupes cyano, de groupes nitro, de groupes carboxy, de groupes carbamoyles, de groupes alkyles en C₁-C₆, de groupes cycloalkyles en C₃-C₈, de groupes alcényles en C₂-C₆, de groupes alcoxy en C₁-C₆, de groupes alkylthio en C₁-C₆, de groupes alkylènes en C₃-C₅, de groupes alkylénoxy en C₂-C₄, de groupes alkylènedioxy en C₁-C₃, de groupes phényles, de groupes phénoxy, de groupes phénylthio, de groupes benzyles, de groupes benzyloxy, de groupes benzoylamino, de groupes alcanoyles en C₂-C₇, de groupes alkoxy-carbonyles en C₂-C₇, de groupes alcanoyloxy en C₂-C₇, de groupes alcanoyl-amino en C₂-C₇, de groupes N-alkylcarbamoyles en C₂-C₇, de groupes N-cycloalkylcarbamoyles en C₄-C₉, de groupes alkylsulfonyles en C₁-C₆, de groupes (alkoxy-carbonyl)méthyles en C₃-C₈, de groupes N-phénylcarbamoyles, de groupes pipéridinocarbonyles, de groupes morpholinocarbonyles, de groupes 1-pyrrolidinylcarbonyles, de groupes bivalents représentés par la formule : NH(C=O)O-, de groupes bivalents représentés par la formule : -NH

(C=S)O-, de groupes amino, de groupes mono(alkyl en C₁-C₆)amino ou de groupes di(alkyl en C₁-C₆)amino ; les substituants du groupe phényle, du groupe cycloalkyle en C₃-C₈, du groupe hétérocyclique aromatique ou du cycle condensé peuvent en outre être substitués par un nombre facultatif d'atomes d'halogène, de groupes hydroxy, de

5 R² est un atome d'hydrogène, un groupe alkyle en C₁-C₆, un groupe alcoxycarbonyle en C₂-C₇, un groupe hydroxy ou un groupe phényle ; le groupe alkyle en C₁-C₆ ou le groupe phényle dans R² peuvent être substitués par un nombre facultatif d'atomes d'halogène, de groupes hydroxy, de groupes alkyles en C₁-C₆ ou de groupes alcoxy en C₁-C₆, à condition que R² ne soit pas un groupe hydroxy lorsque j est 0 ;

j est un nombre entier de 0 à 2 ;

10 k est un nombre entier de 0 à 2 ;

m est un nombre entier de 2 à 4 ;

n est 0 ou 1 ;

15 R³ est un atome d'hydrogène ou un groupe alkyle en C₁-C₆ (qui peut être substitué par un ou deux groupes phényles qui peuvent respectivement être substitués par un nombre facultatif d'atomes d'halogène, de groupes hydroxy, de groupes alkyles en C₁-C₆ ou de groupes alcoxy en C₁-C₆, identiques ou différents) ;

20 R⁴ et R⁵ sont identiques ou différents et sont chacun un atome d'hydrogène, un groupe hydroxy, un groupe phényle ou un groupe alkyle en C₁-C₆ ; le groupe alkyle en C₁-C₆ dans R⁴ et R⁵ peut être substitué par un nombre facultatif d'atomes d'halogène, de groupes hydroxy, de groupes cyano, de groupes nitro, de groupes carboxy, de groupes carbamoyles, de groupes mercapto, de groupes guanidino, de groupes cycloalkyles en C₃-C₈, de groupes alcoxy en C₁-C₆, de groupes alkylthio en C₁-C₆, groupes phényles (qui peuvent être substitués par un nombre facultatif d'atomes d'halogène, de groupes hydroxy, de groupes alkyles en C₁-C₆, de groupes alcoxy en C₁-C₆ ou de groupes benzyloxy), de groupes phénoxy, de groupes benzyloxy, de groupes benzyloxycarbonyles, de groupes alcanoyles en C₂-C₇, de groupes alcoxycarbonyles en C₂-C₇, de groupes alcanoyloxy en C₂-C₇, de groupes alcanoylamino en C₂-C₇, de groupes N-alkylcarbamoyles en C₂-C₇, de groupes alkylsulfonyles en C₁-C₆, de groupes amino, de

25 groupes mono(alkyl en C₁-C₆)amino, de groupes di(alkyl en C₁-C₆)amino ou groupes hétérocycliques aromatiques (ayant de 1 à 3 atomes d'oxygène, atomes de soufre et/ou atomes d'azote en tant que des hétéroatomes) ou cycles condensés formés par la condensation de groupes hétérocycliques aromatiques (ayant de 1 à 3 atomes d'oxygène, atomes de soufre et/ou atomes de nitrogène en tant que les hétéroatomes) avec des cycles benzènes ou R⁴ et R⁵ peuvent conjointement former un hydrocarbure cyclique à 3 à 6 membres ;

30 p est 0 ou 1 ;

q est 0 ou 1 ;

G est un groupe représenté par -CO-, -SO₂-, -CO-O-, -NR⁷-CO-, -CO-NR⁷-, NH-CO-NH-, -NH-CS-NH-, -NR⁷-SO₂-, -SO₂-NR⁷-, -NH-CO-O- ou -O-CO-NH-, dans lesquelles R⁷ est un atome d'hydrogène ou un groupe alkyle en C₁-C₆ ou R⁷, conjointement avec R⁵, peut former un groupe alkylène en C₂-C₅;

35 R⁶ est un groupe phényle, un groupe cycloalkyle en C₃-C₈, un groupe cycloalcényle en C₃-C₆, un groupe benzyle ou un groupe hétérocyclique aromatique ayant de 1 à 3 atomes d'oxygène, atomes de soufre et/ou atomes d'azote en tant qu'hétéroatomes ; le groupe phényle, le groupe benzyle ou le groupe hétérocyclique aromatique dans R⁶ peuvent être condensés avec un cycle benzène ou un groupe hétérocyclique aromatique ayant de 1 à 3 atomes d'oxygène, atomes de soufre et/ou atomes d'azote en tant que des hétéroatomes pour former un cycle condensé ;

40 le groupe phényle, le groupe cycloalkyle en C₃-C₈, le groupe cycloalcényle en C₃-C₆, le groupe benzyle, le groupe hétérocyclique aromatique ou le cycle condensé dans R⁶ ci-dessus peuvent être substitués par un nombre facultatif d'atomes d'halogène, de groupes hydroxy, de groupes mercapto, de groupes cyano, de groupes nitro, de groupes thiocyanato, de groupes carboxy, de groupes carbamoyles, de groupes trifluorométhyles, de groupes alkyles en C₁-C₆, de groupes cycloalkyles en C₃-C₈, de groupes alcényles en C₂-C₆, de groupes alcoxy en C₁-C₆, de

45 groupes cycloalcoxy en C₃-C₈, de groupes alkylthio en C₁-C₆, de groupes alkylènedioxy en C₁-C₃, de groupes phényles, de groupes phénoxy, de groupes phénylamino, de groupes benzyles, de groupes benzoyles, de groupes phénylsulfinyles, de groupes phénylsulfonyles, de groupes 3-phényluréido, de groupes alcanoyles en C₂-C₇, de groupes alcoxycarbonyles en C₂-C₇, de groupes alcanoyloxy en C₂-C₇, de groupes alcanoylamino en C₂-C₇, de groupes N-alkylcarbamoyles en C₂-C₇, de groupes alkylsulfonyles en C₁-C₆, de groupes phénylcarbamoyles, de

50 groupes N,N-di(alkyl en C₁-C₆)sulfamoyles, de groupes amino, de groupes mono(alkyl en C₁-C₆)amino, de groupes di(alkyl en C₁-C₆)amino, de groupes benzylamino, de groupes (alcoxycarbonyl)amino en C₂-C₇, de groupes (alkylsulfonyl)amino en C₁-C₆ ou de groupes bis(alkylsulfonyl en C₁-C₆)amino ; les substituants du groupe phényle, du groupe cycloalkyle en C₃-C₈, du groupe cycloalcényle en C₃-C₆, du groupe benzyle, du groupe hétérocyclique aromatique ou du cycle condensé peuvent en outre être substitués par un nombre facultatif d'atomes d'halogène,

55 de groupes cyano, de groupes hydroxy, de groupes amino, de groupes trifluorométhyles, de groupes alkyles en C₁-C₆, de groupes alcoxy en C₁-C₆, de groupes alkylthio en C₁-C₆, de groupes mono(alkyl en C₁-C₆)amino ou de groupes di(alkyl en C₁-C₆)amino.

Fig. 1

12th Week after Immunization

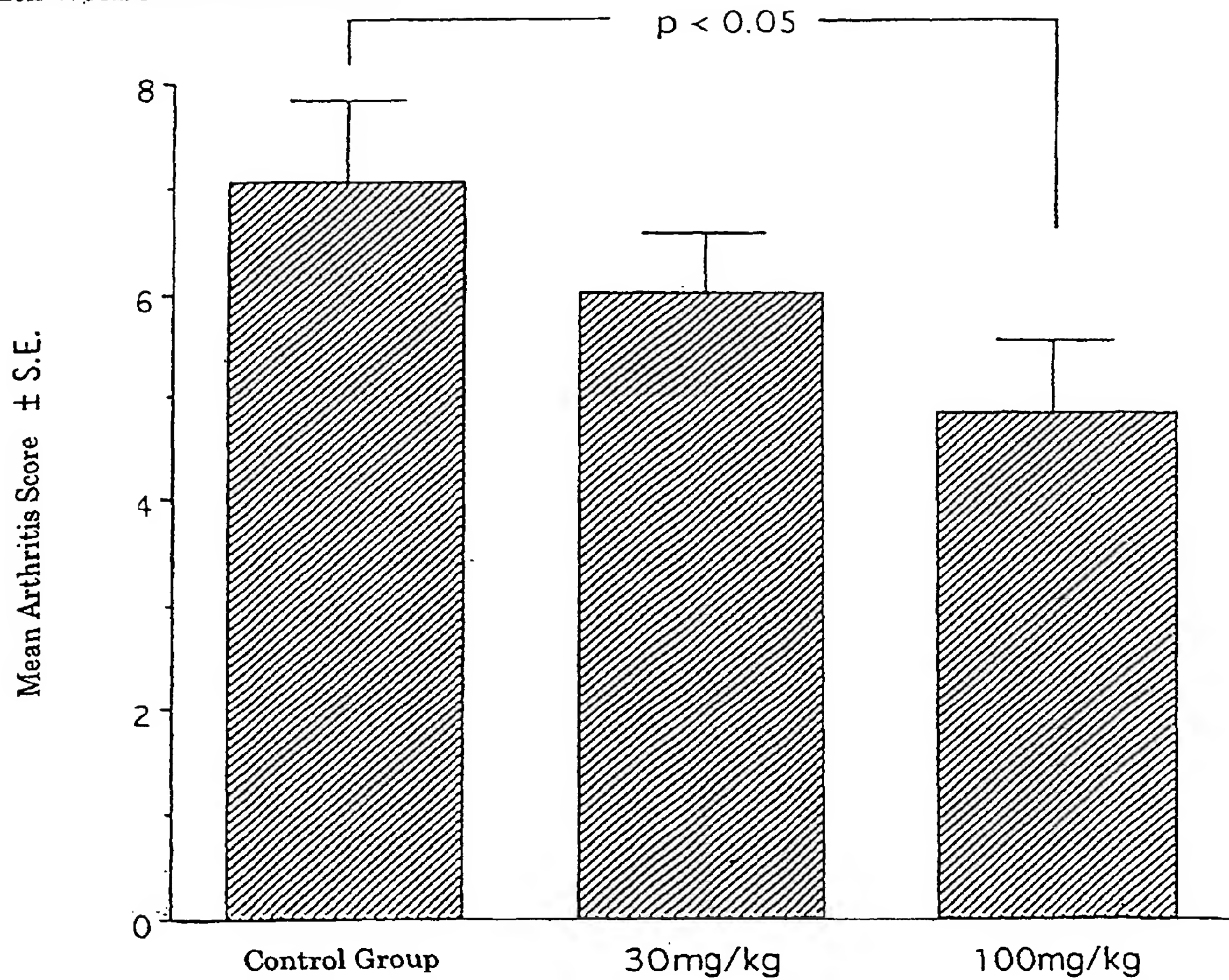


Fig. 2

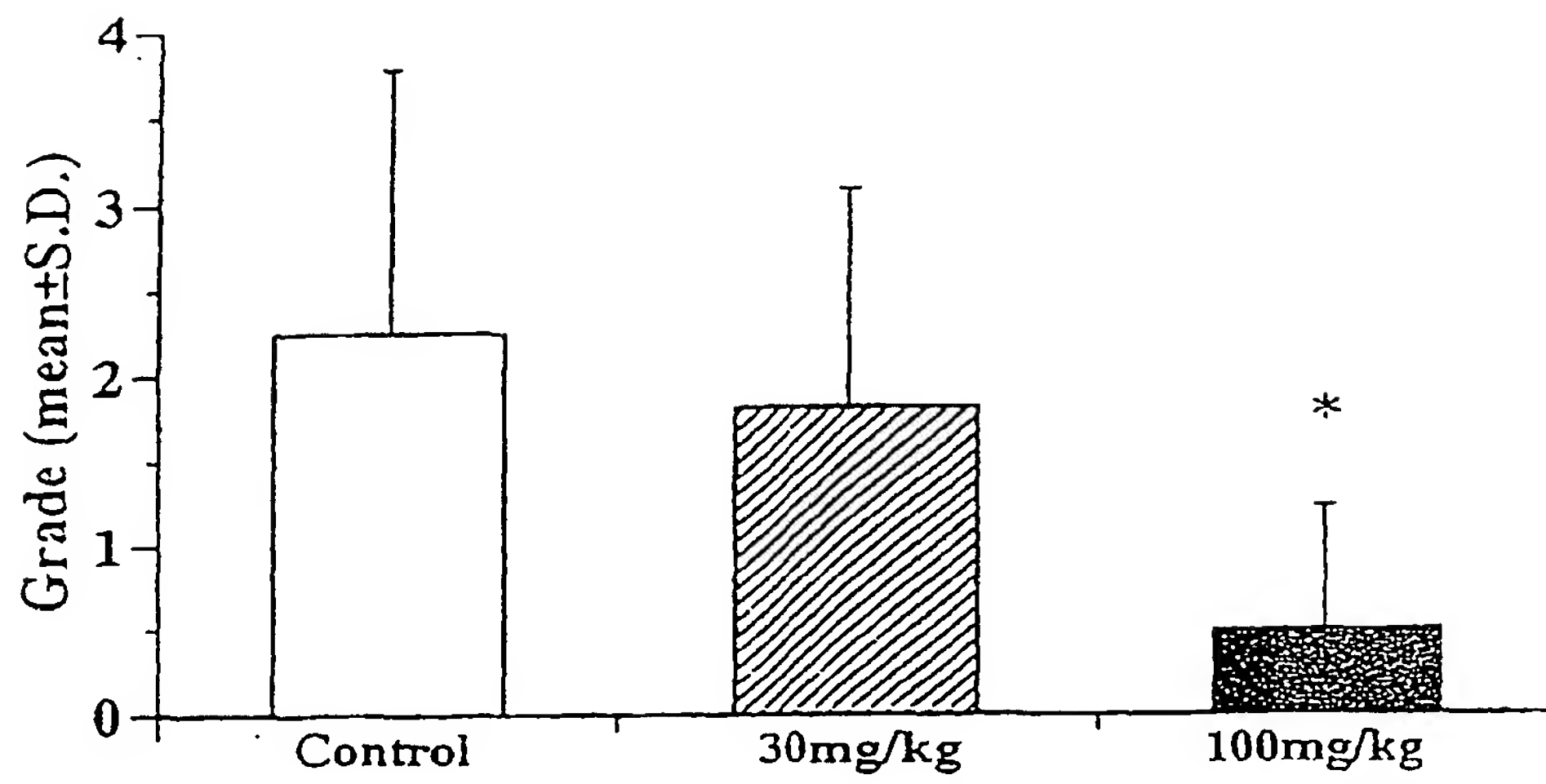


Fig. 3

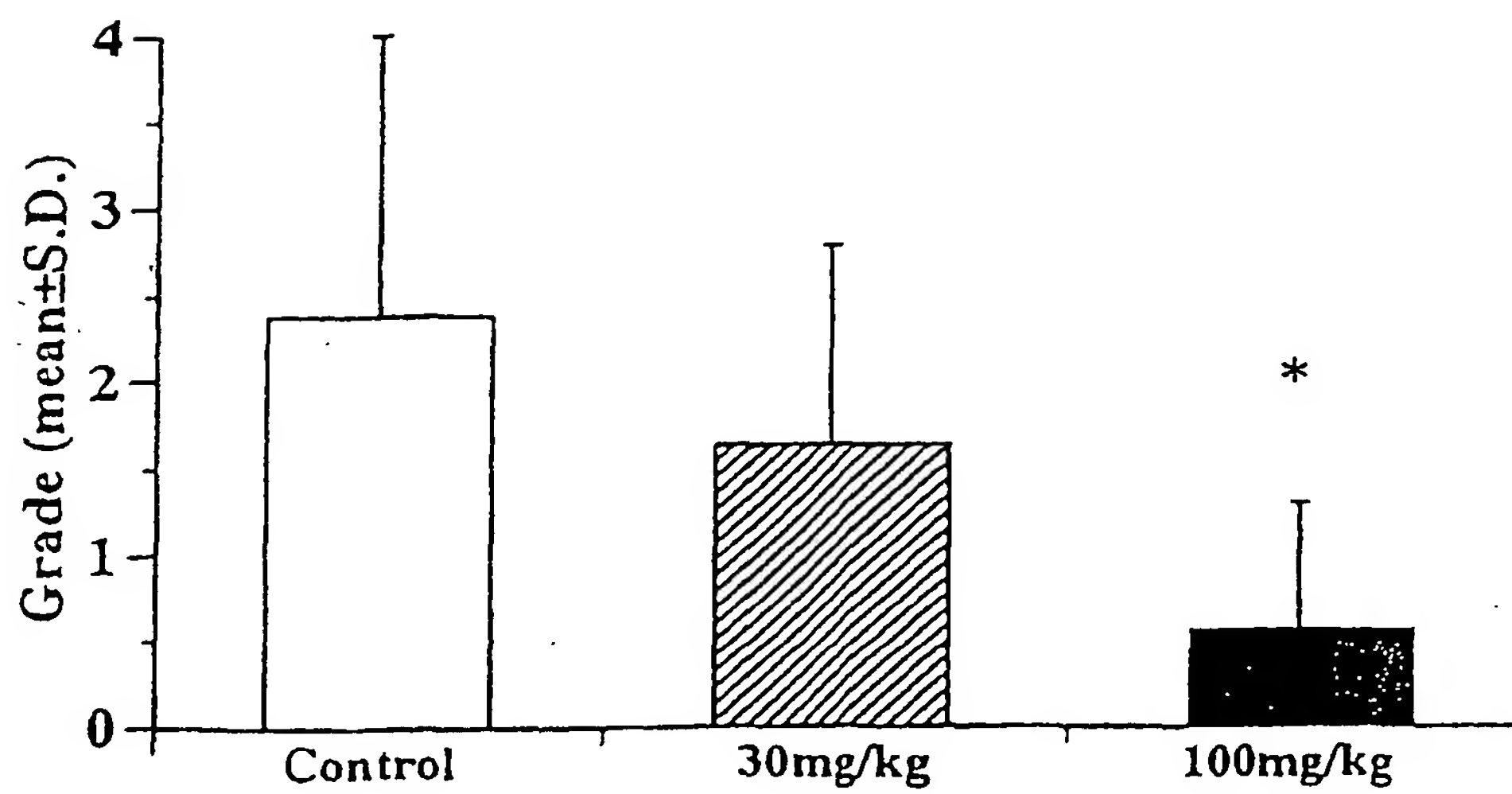


Fig. 4

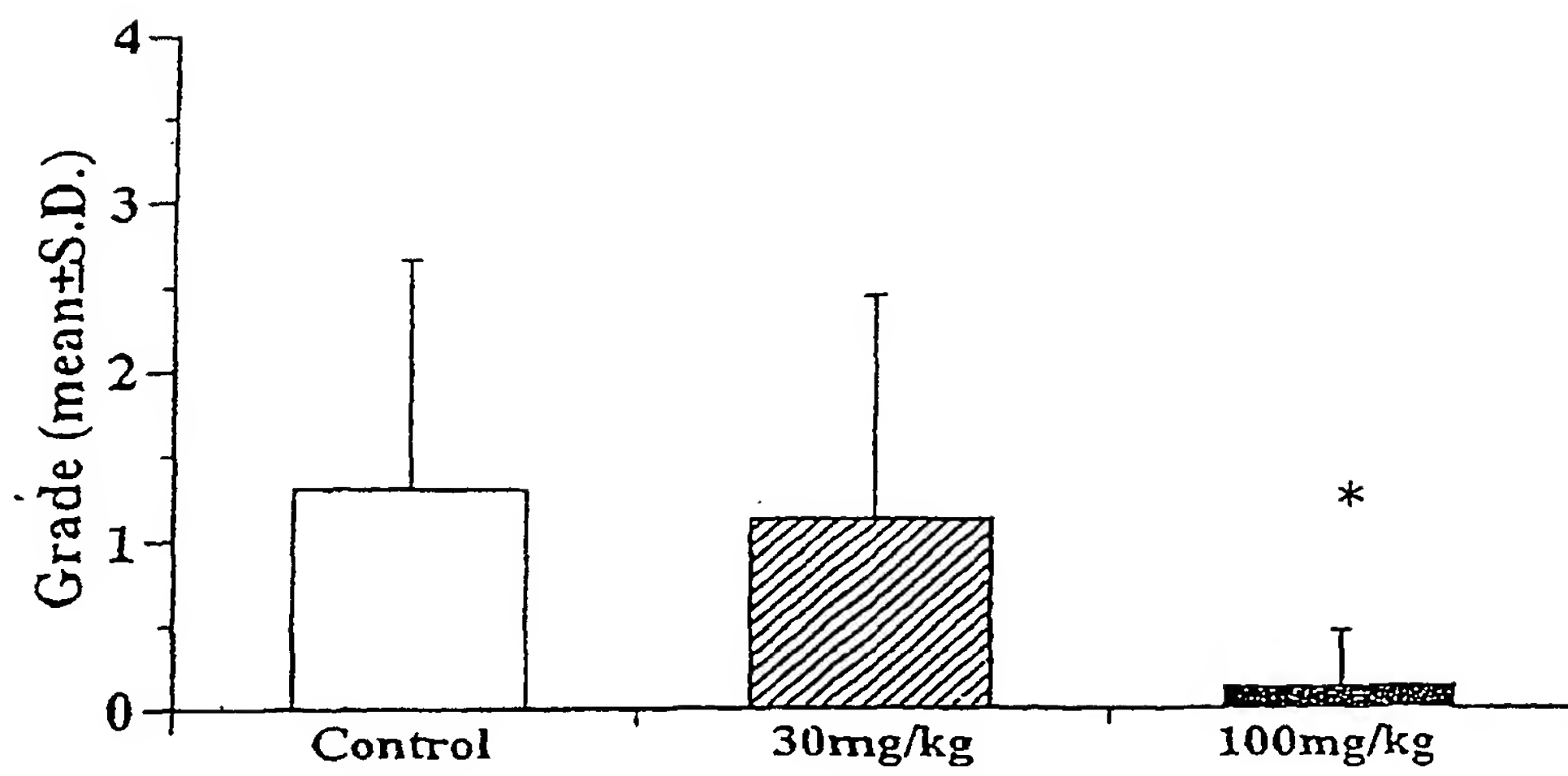


Fig. 5

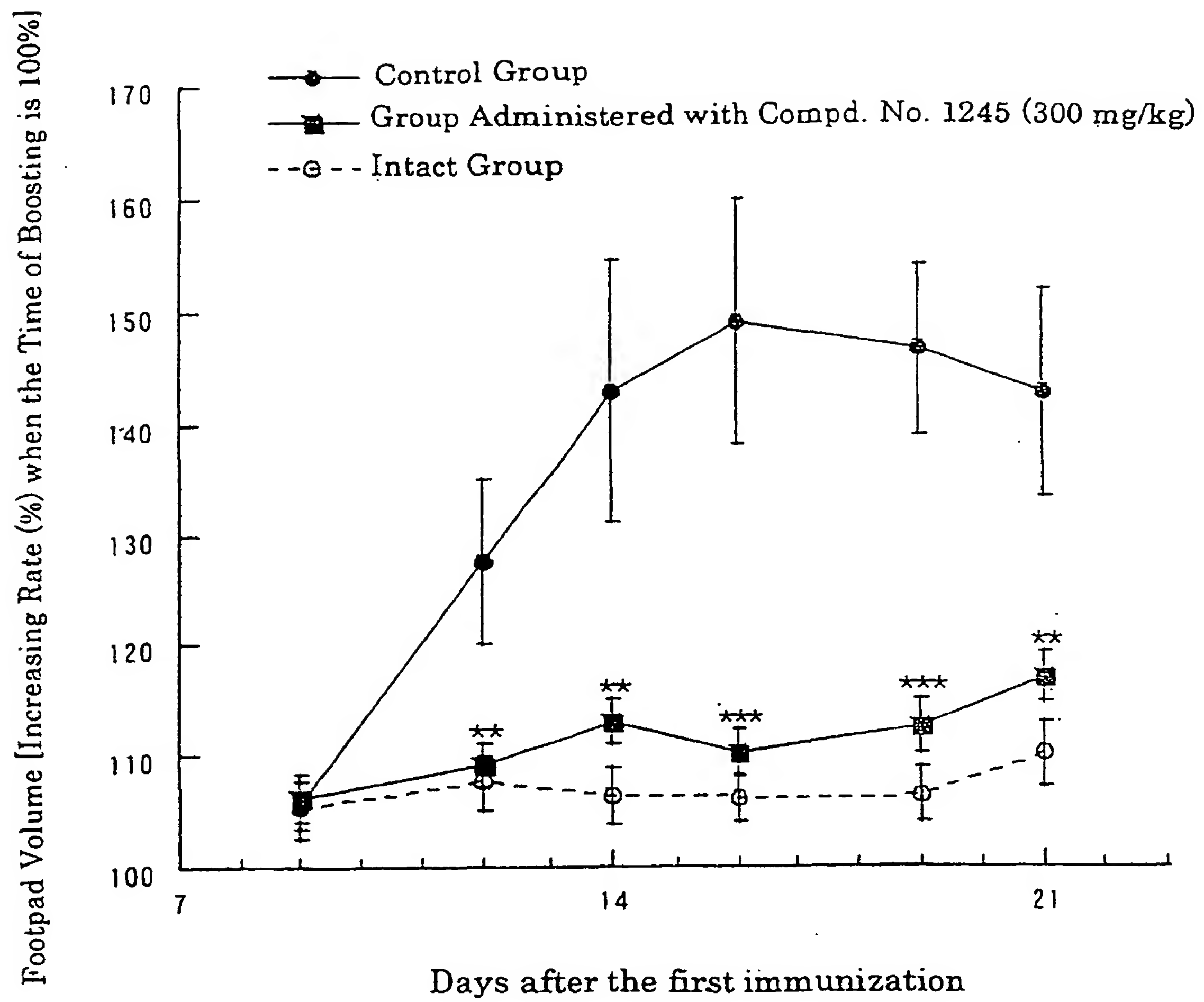


Fig. 6

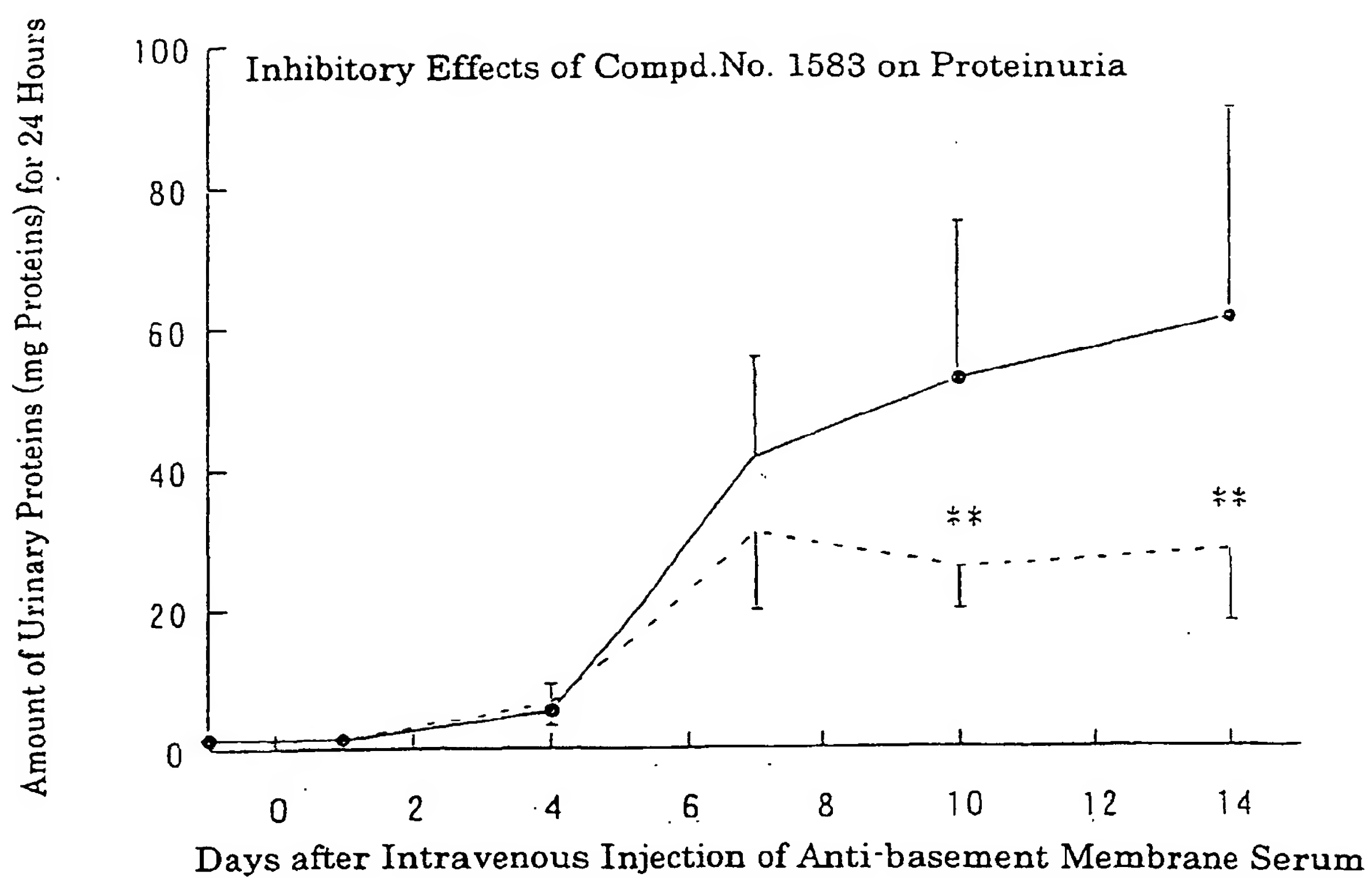


Fig. 7

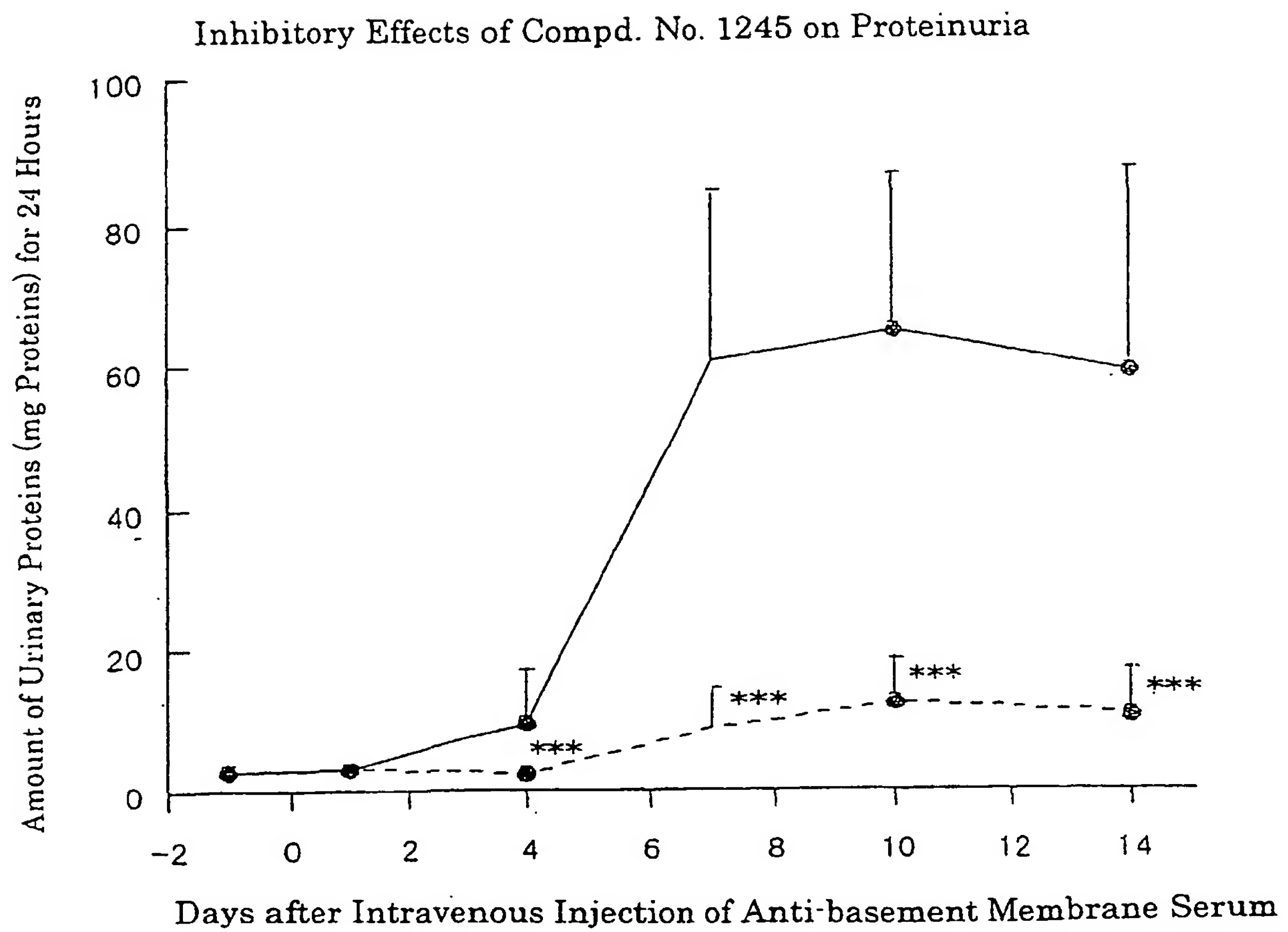


Fig. 8

